

FIG. 1

			P22					Y91					L265				
Class I	HDLP	P	L	G	G	Y	E	N	P				Y		L		
	HDAC1	P	M	G	-	E	D	C	P				R		L		
	HDAC2	P	M	G	-	E	D	C	P				R		L		
	HDAC3	P	M	G	-	D	D	C	P				R		L		
	HDAC8	A	K	G	-	Y	D	C	P				P		M		
	HDAC4	P	E	G	V	D	S	D	T				P		L		
	HDAC5	P	E	G	V	D	S	D	T				P		L		
	HDAC6(a)	P	E	-	-	-	-	D	S				P		K		
Class II	HDAC6(b)	P	E	-	-	-	-	D	S				P		L		
	HDAC7	P	E	G	G	D	T	D	T				P		L		

FIG. 2

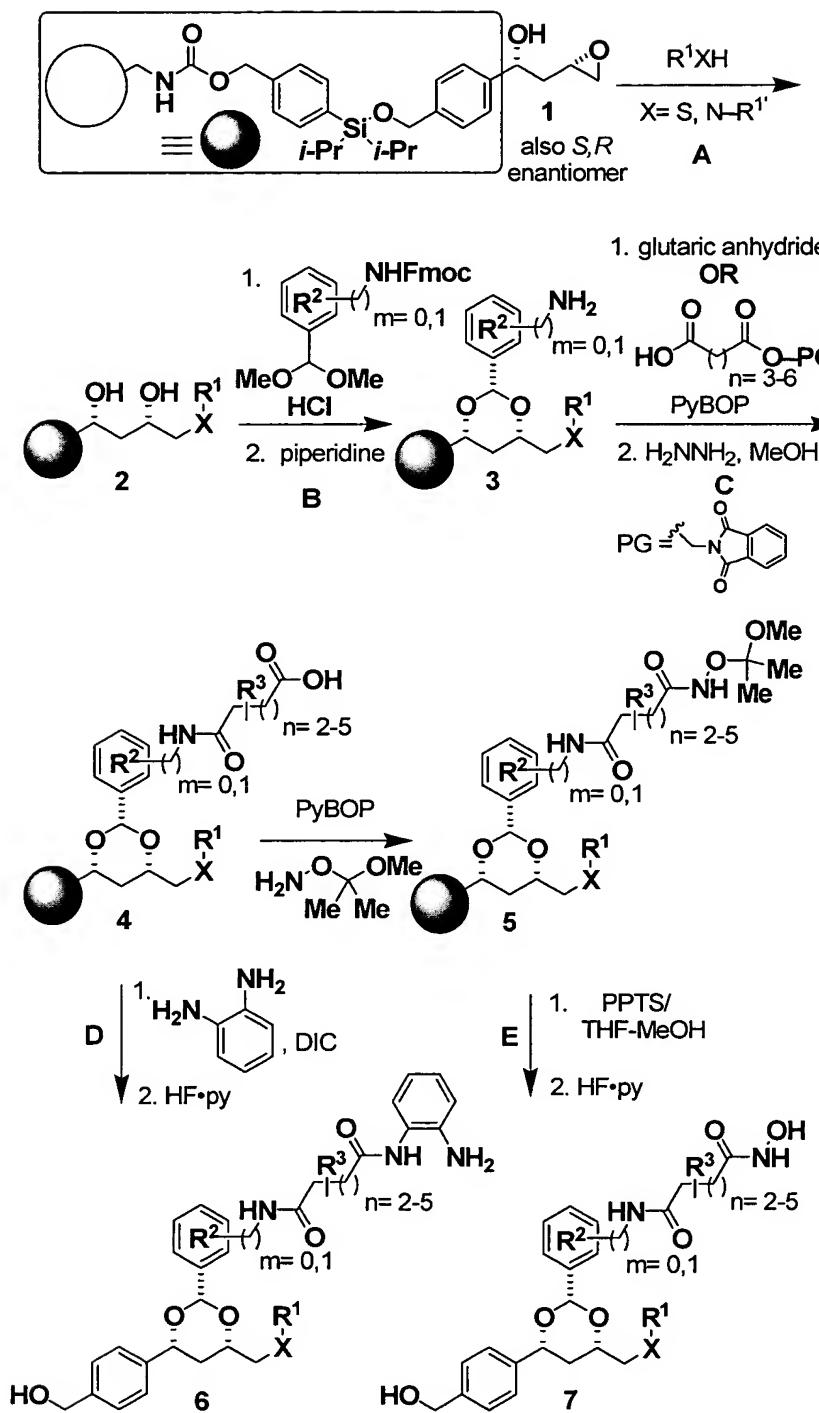
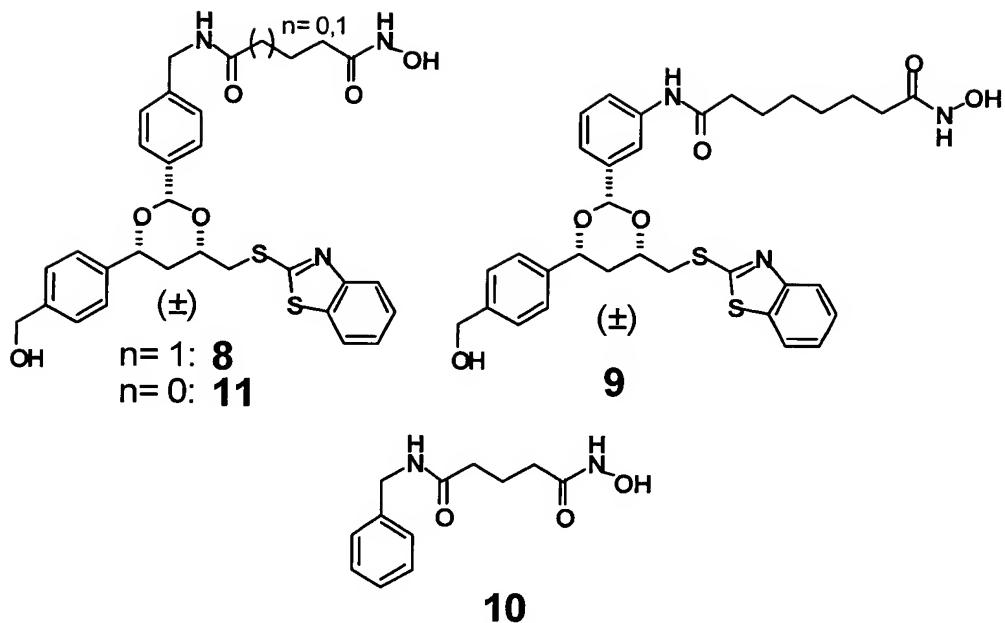


FIG. 3

Compound	HDAC1	HDAC6
8	1.2 ± 0.5	0.9 ± 0.2
9	1.7 ± 1.2	1.1 ± 0.1
10	1.5 ± 0.2	0.38 ± 0.04

FIG. 4

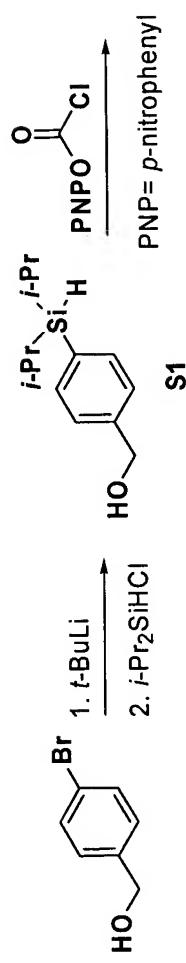
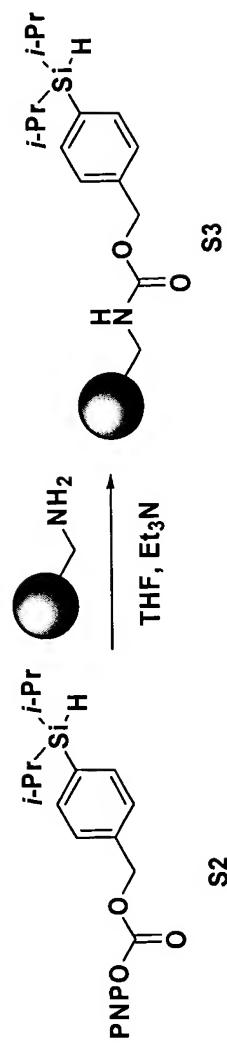


FIG. 5



S11b

S14b

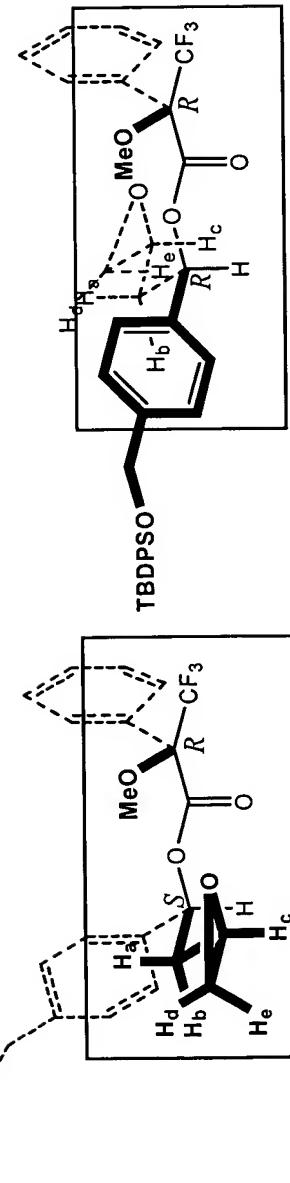


FIG. 6

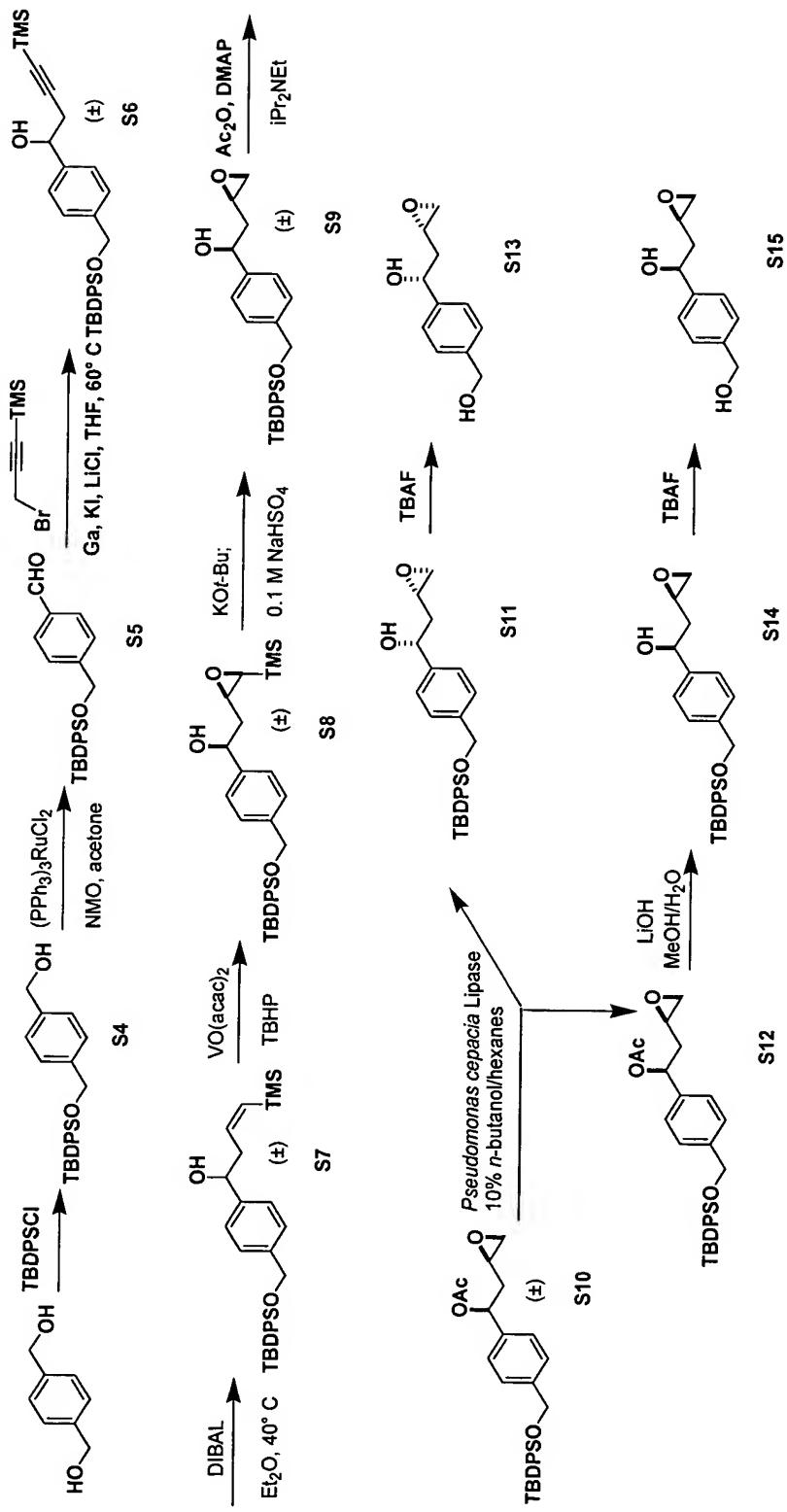


FIG. 7

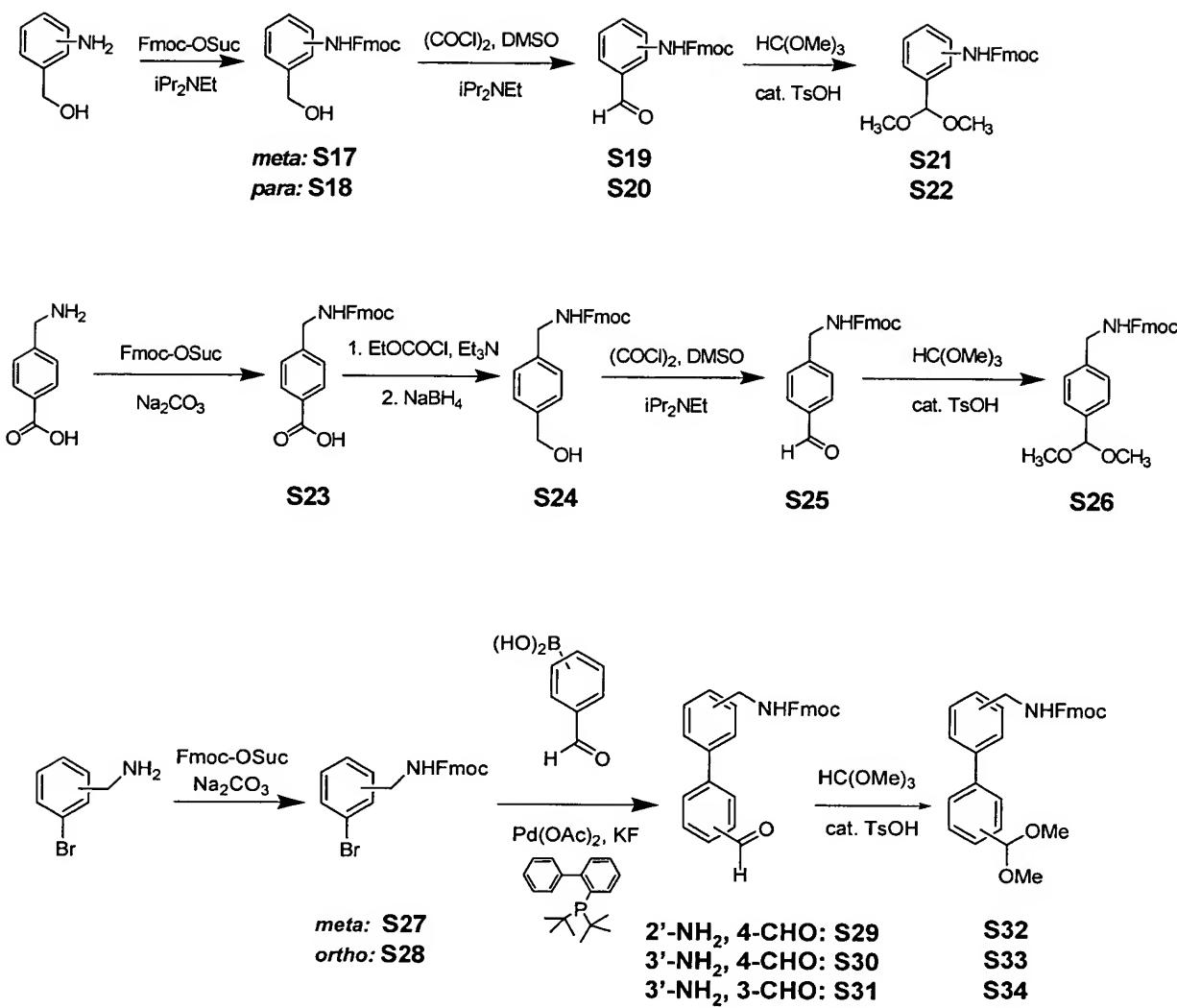




FIG. 8A

FIG. 8B

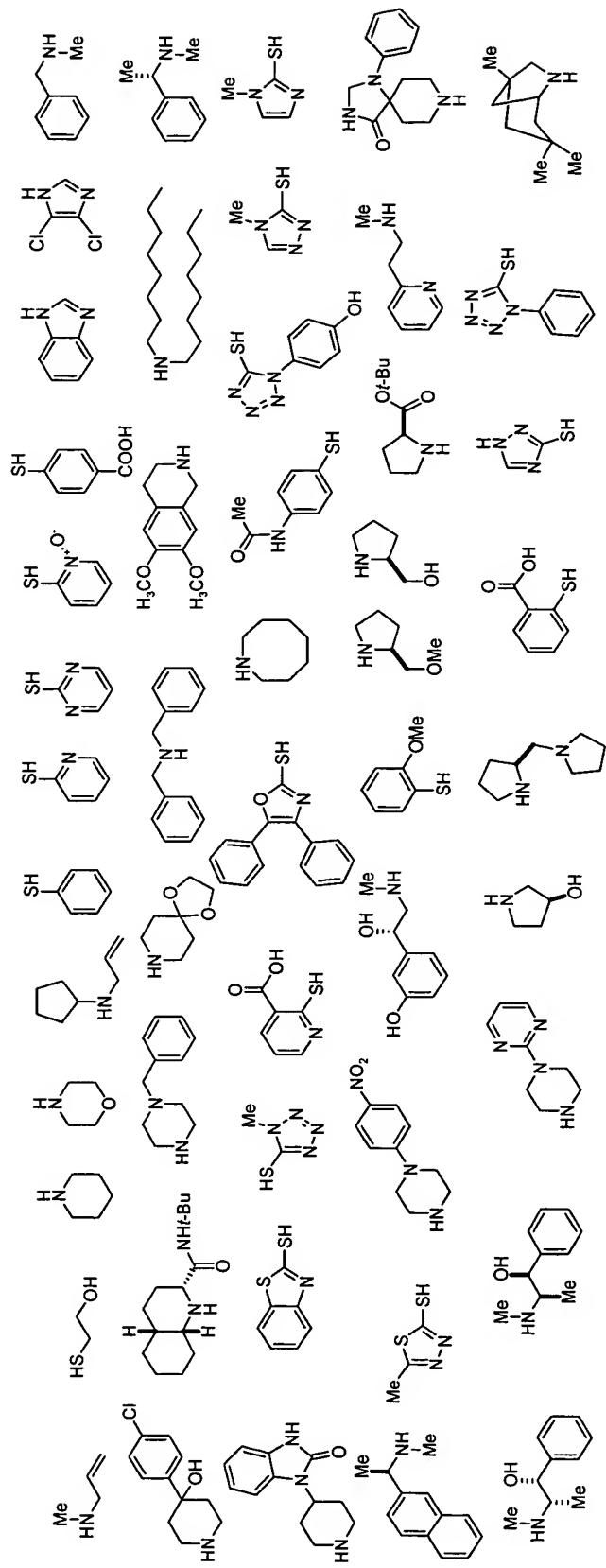


FIG. 8C

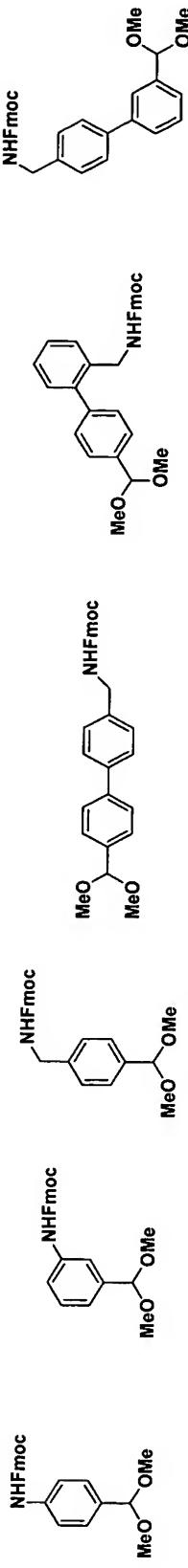


FIG. 8D

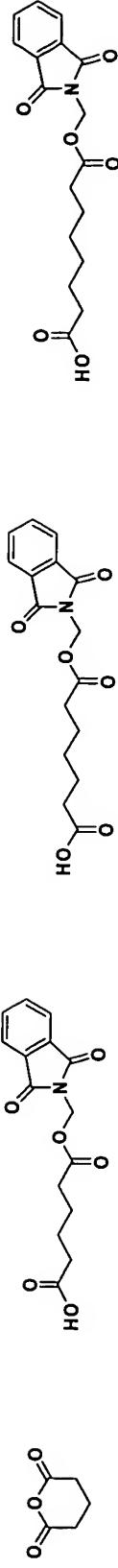


FIG. 9A

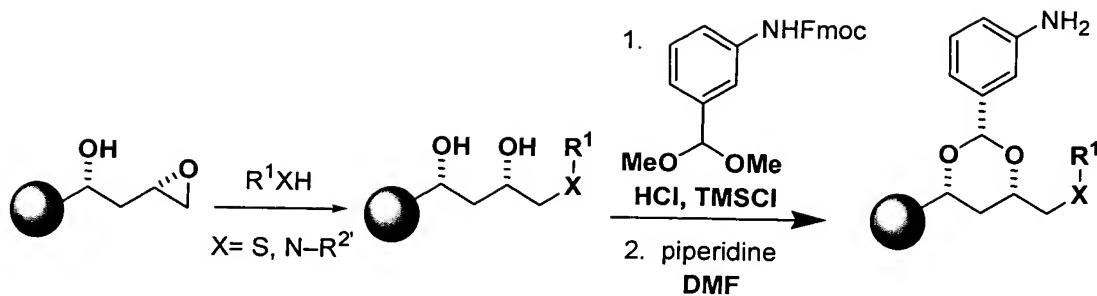


FIG. 9B

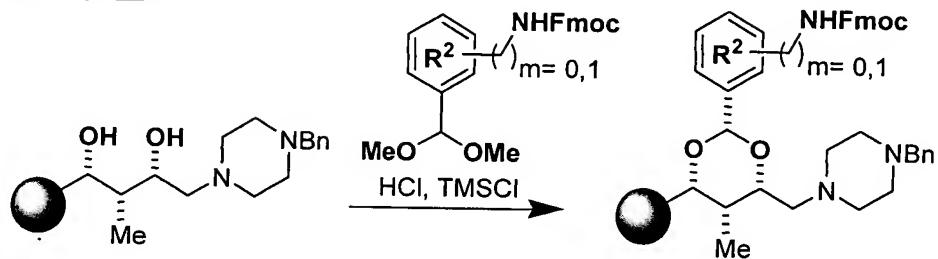


FIG. 9C

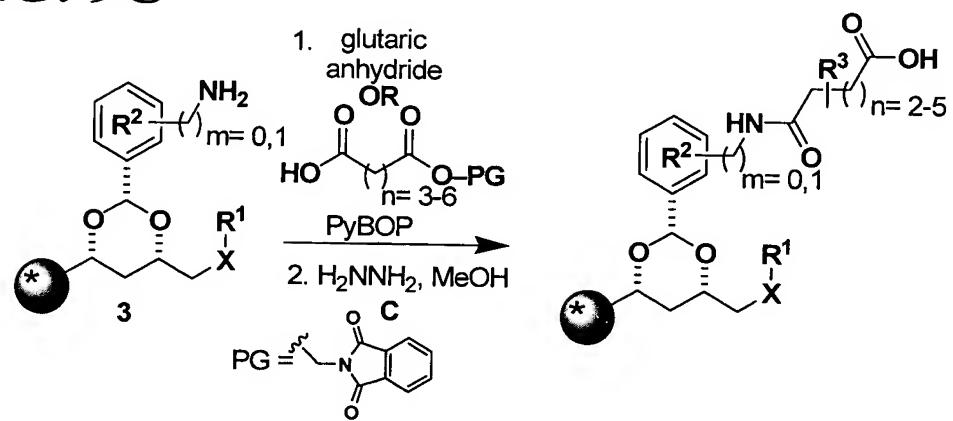
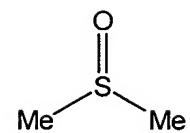
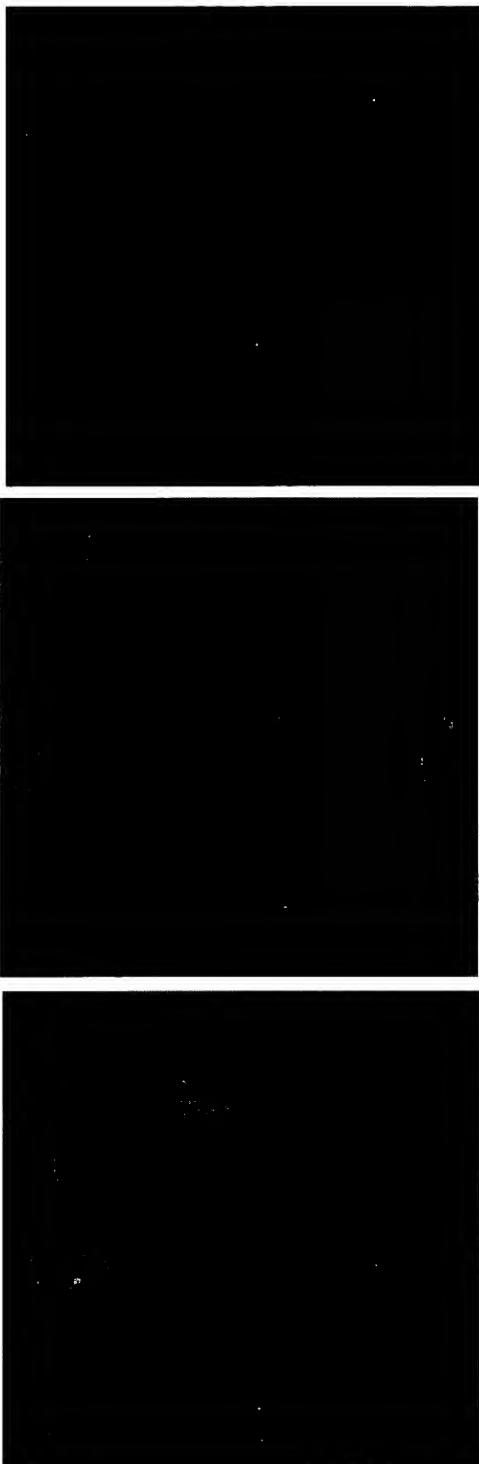
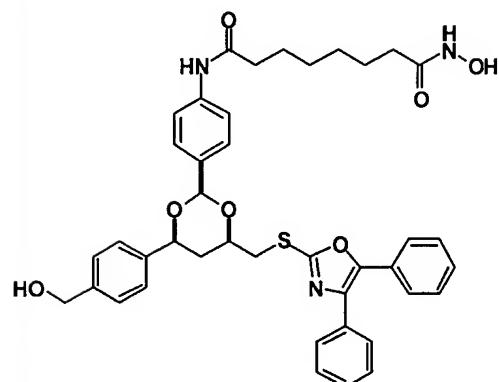


FIG. 10

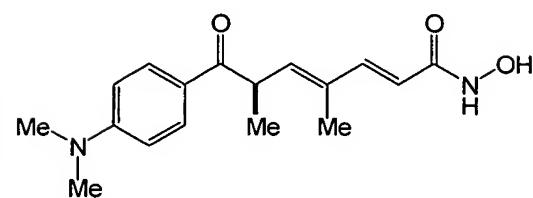
Glutaraldehyde/TX-100 fixation



Dimethylsulfoxide (0.1%)



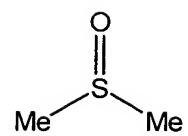
JCWII144 (200 nM)



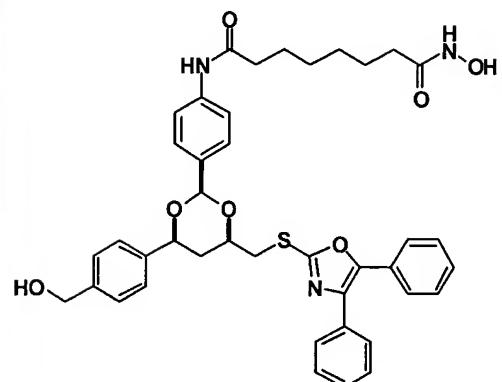
trichostatin (100 nM)

FIG. 11

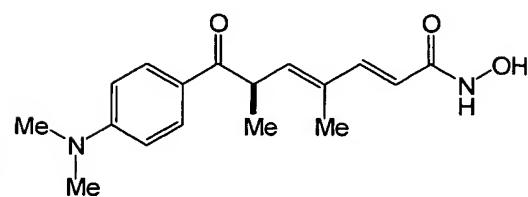
95% ethanol/5% acetic acid fixation



Dimethylsulfoxide (0.1%)



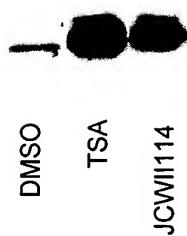
JCWII144 (2 μ M)



trichostatin (1 μ M)

FIG. 12

Acetylated
Tubulin



Acetylated
Histone H3



Notes:

TSA treatment at 300nM
JCWII114 treatment at 2 μ M

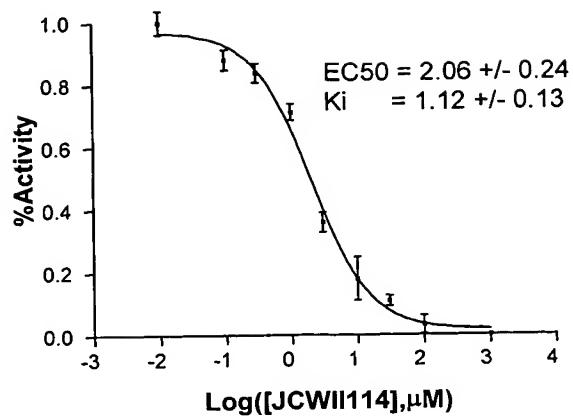
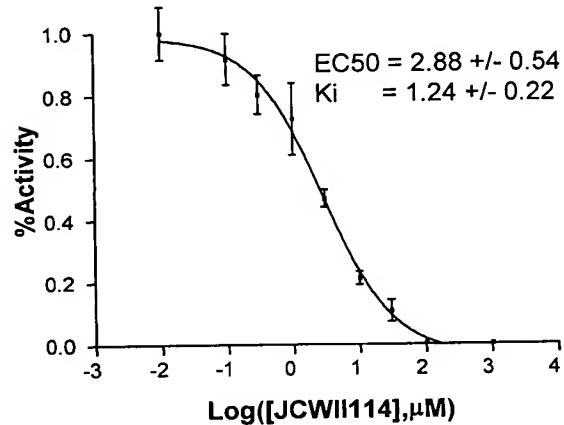
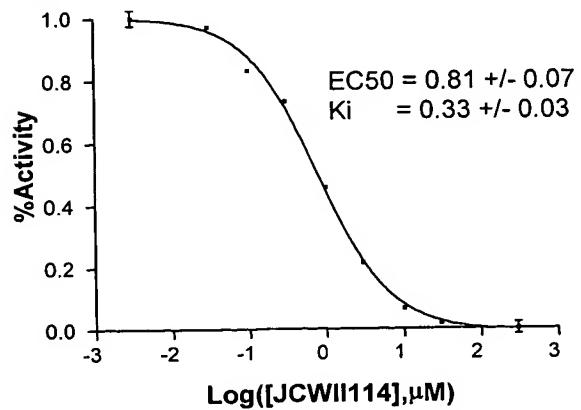
FIG. 13A**FIG. 13B****FIG. 13C**

FIG. 14

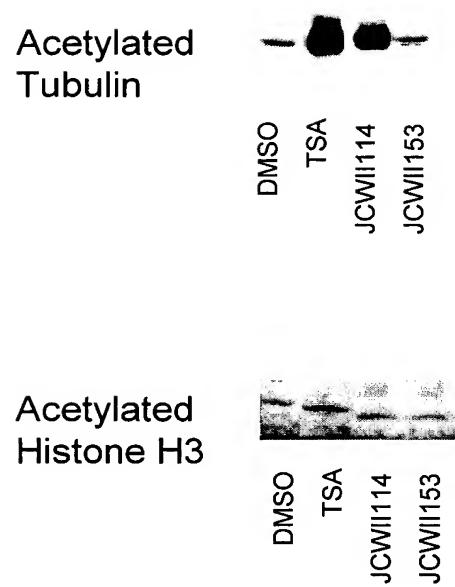


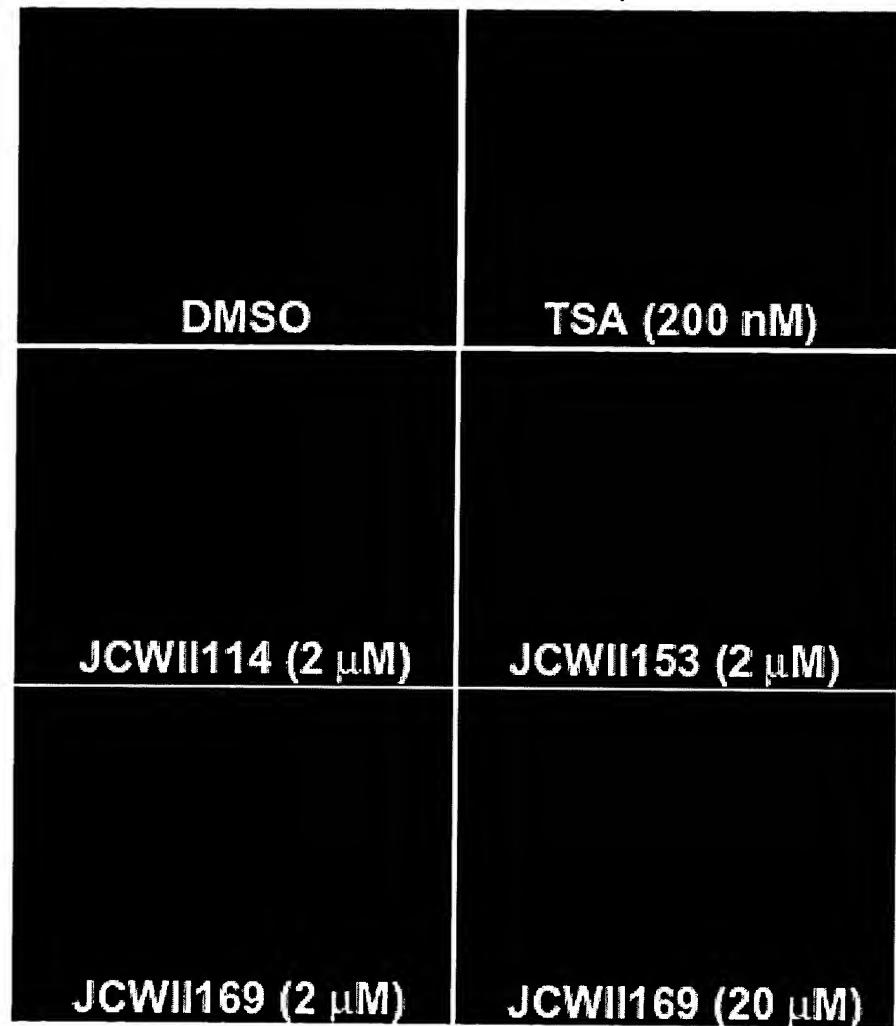
FIG. 15

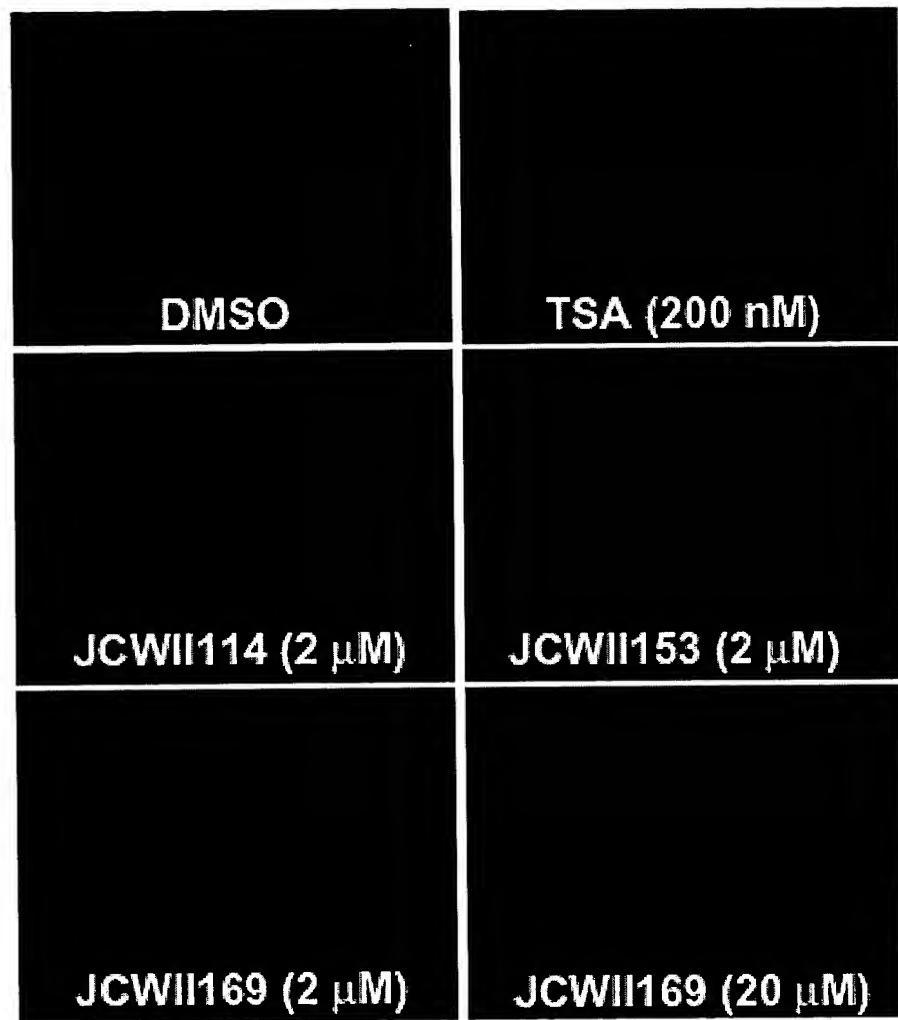
FIG. 16

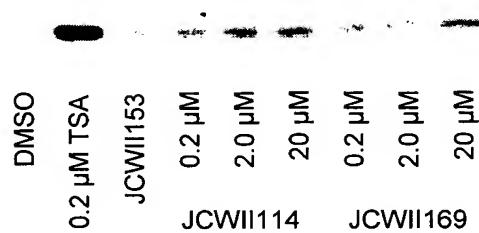
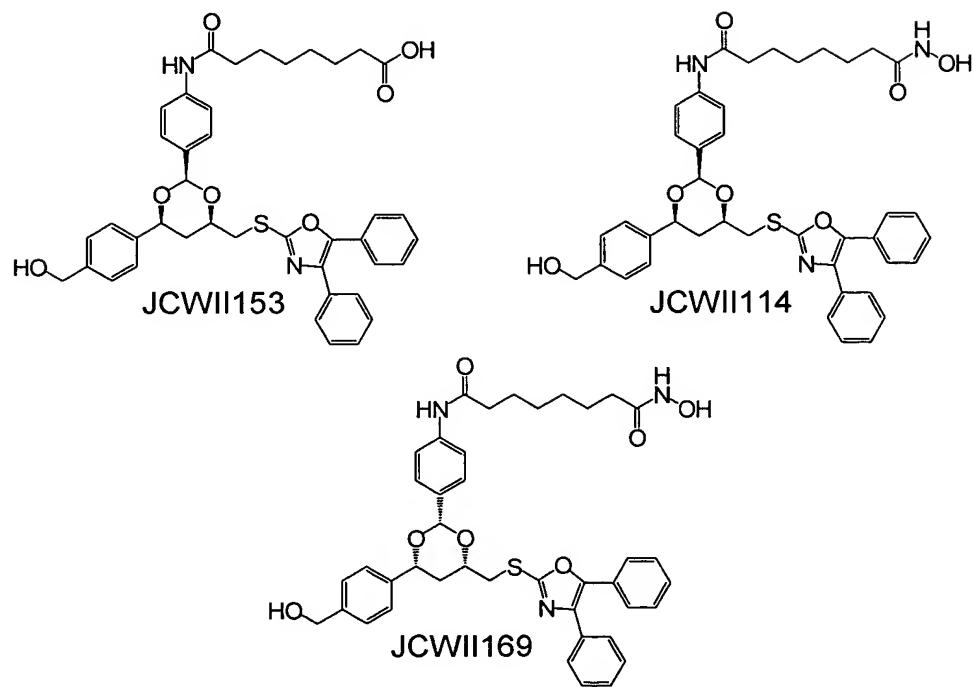
FIG. 17A**FIG. 17B****FIG. 17C**

FIG. 18

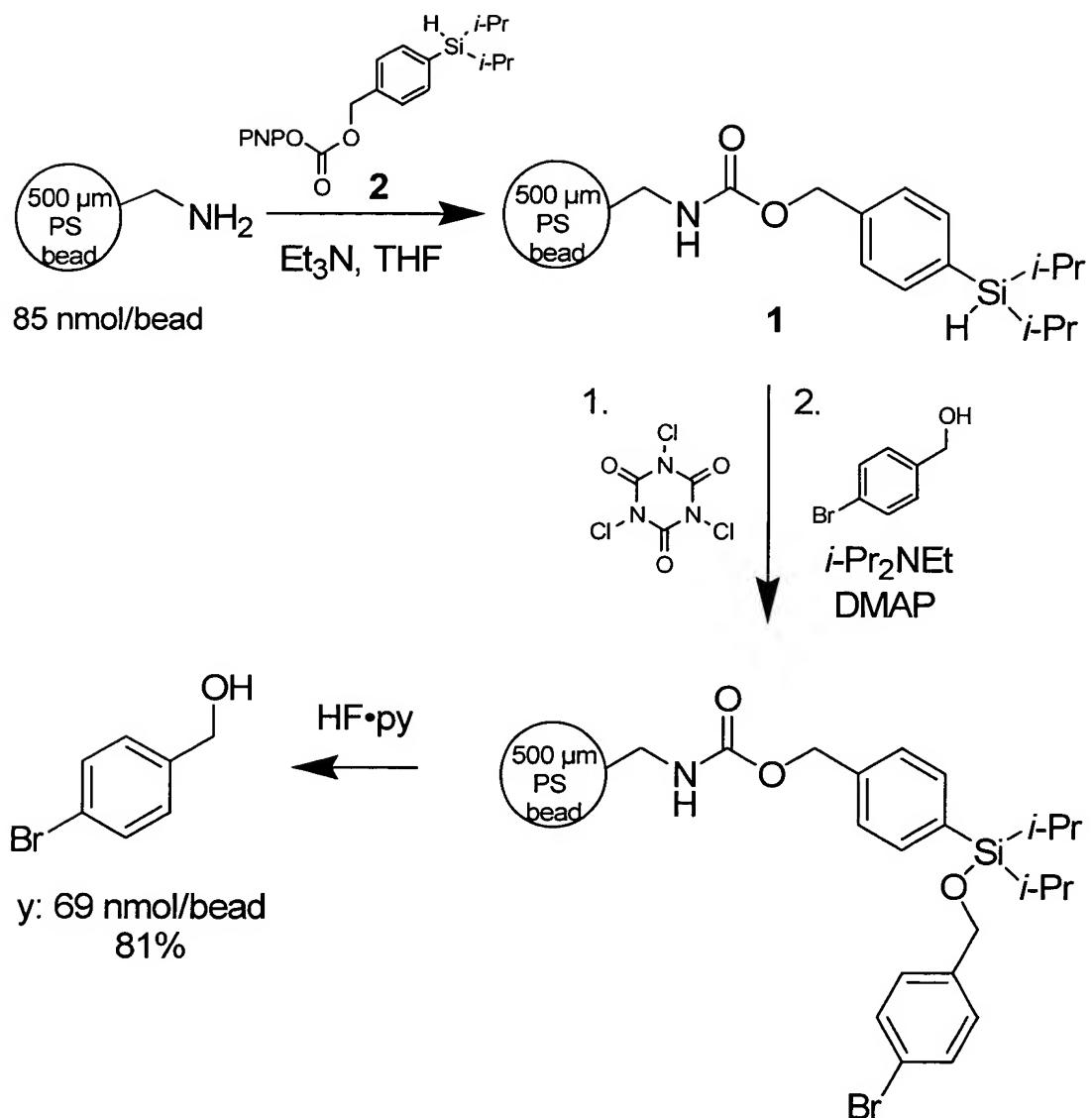


FIG. 19

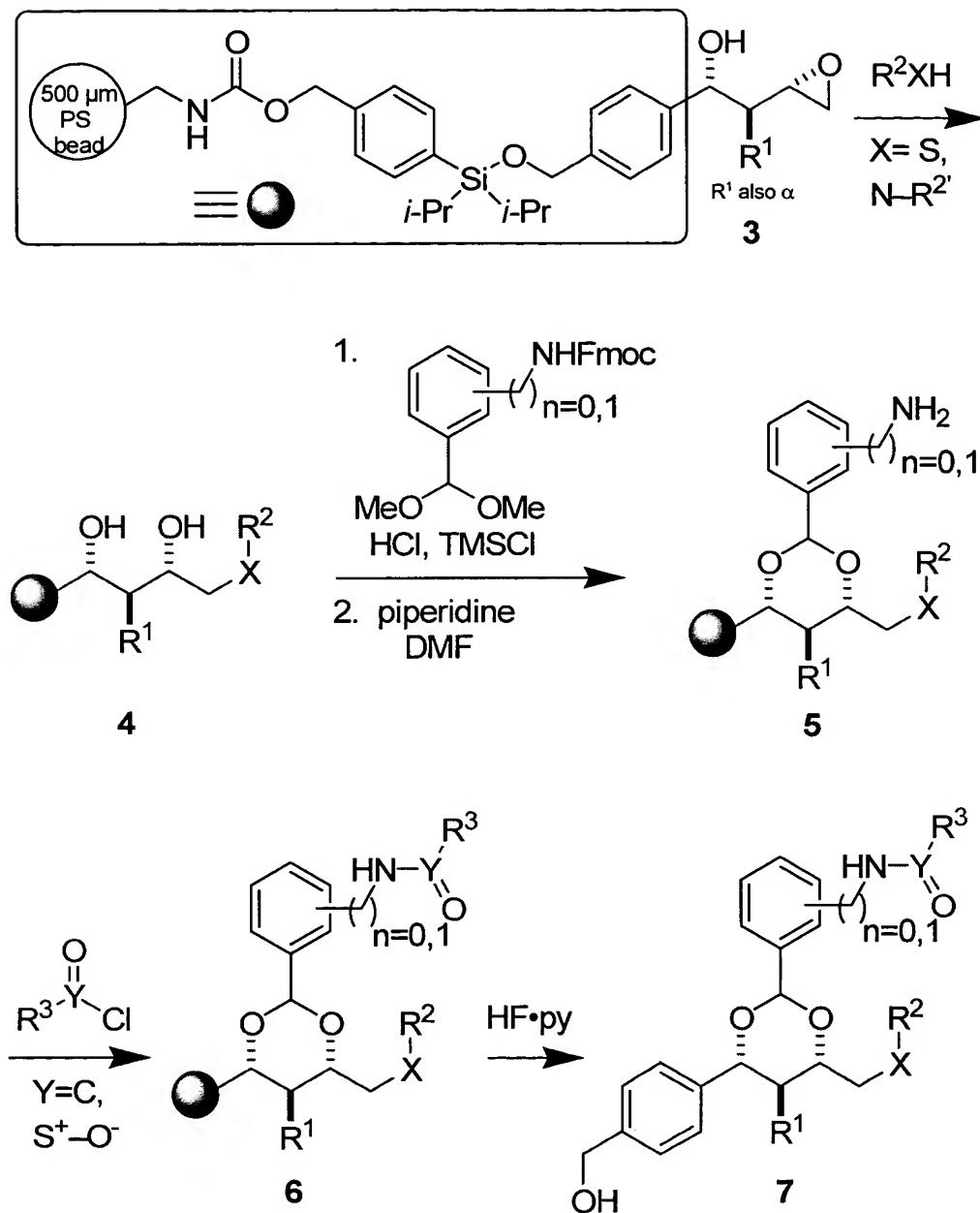


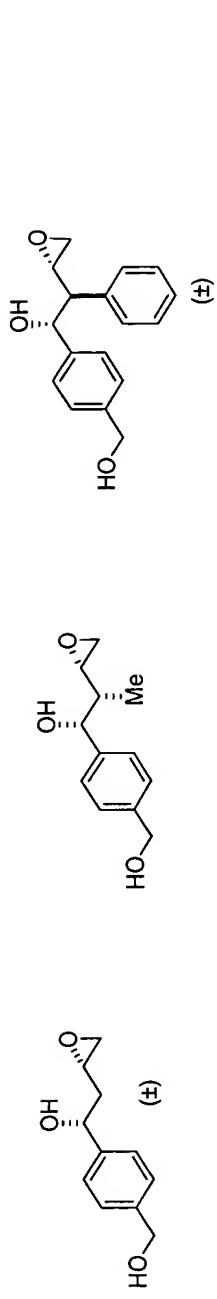
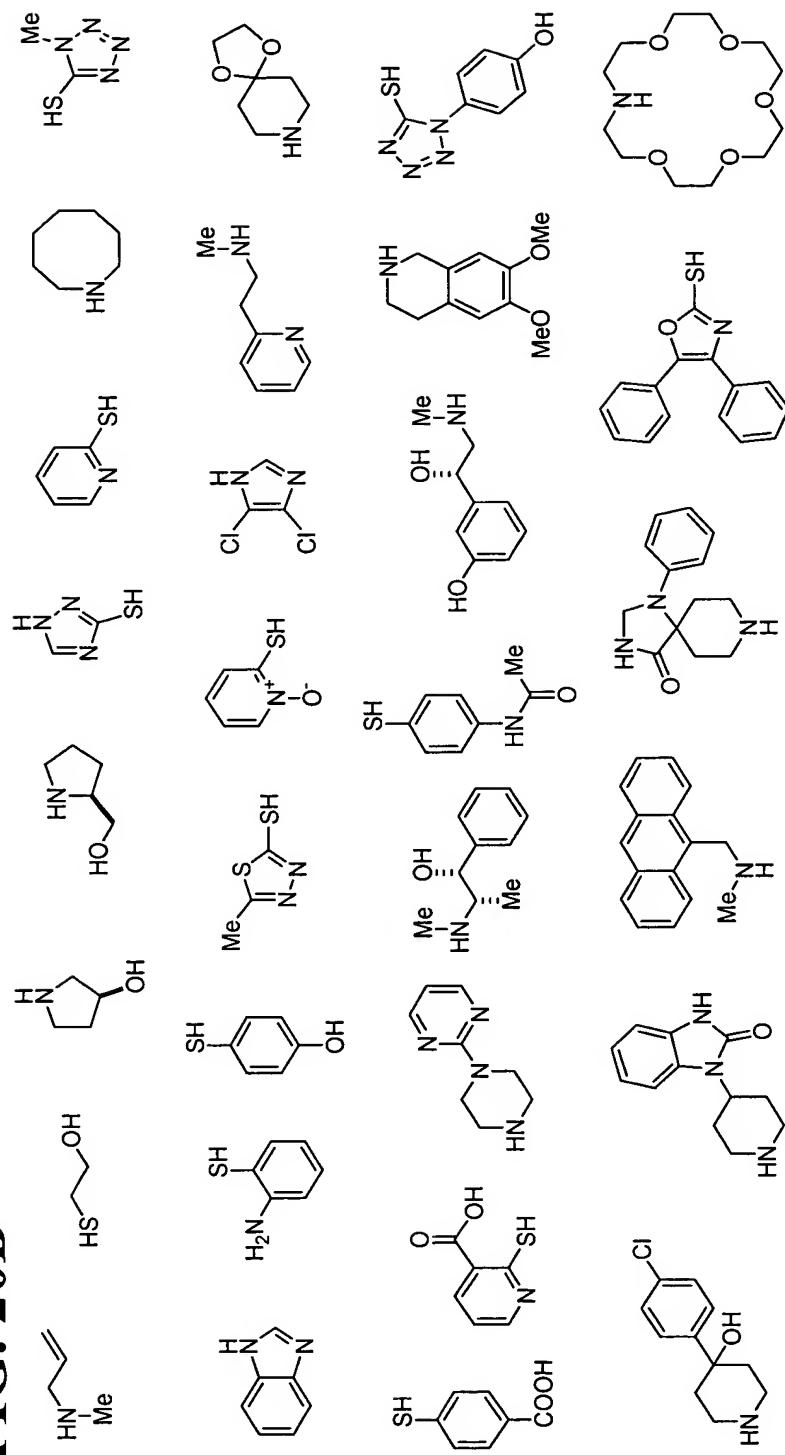
FIG. 20A**FIG. 20B**

FIG. 20C

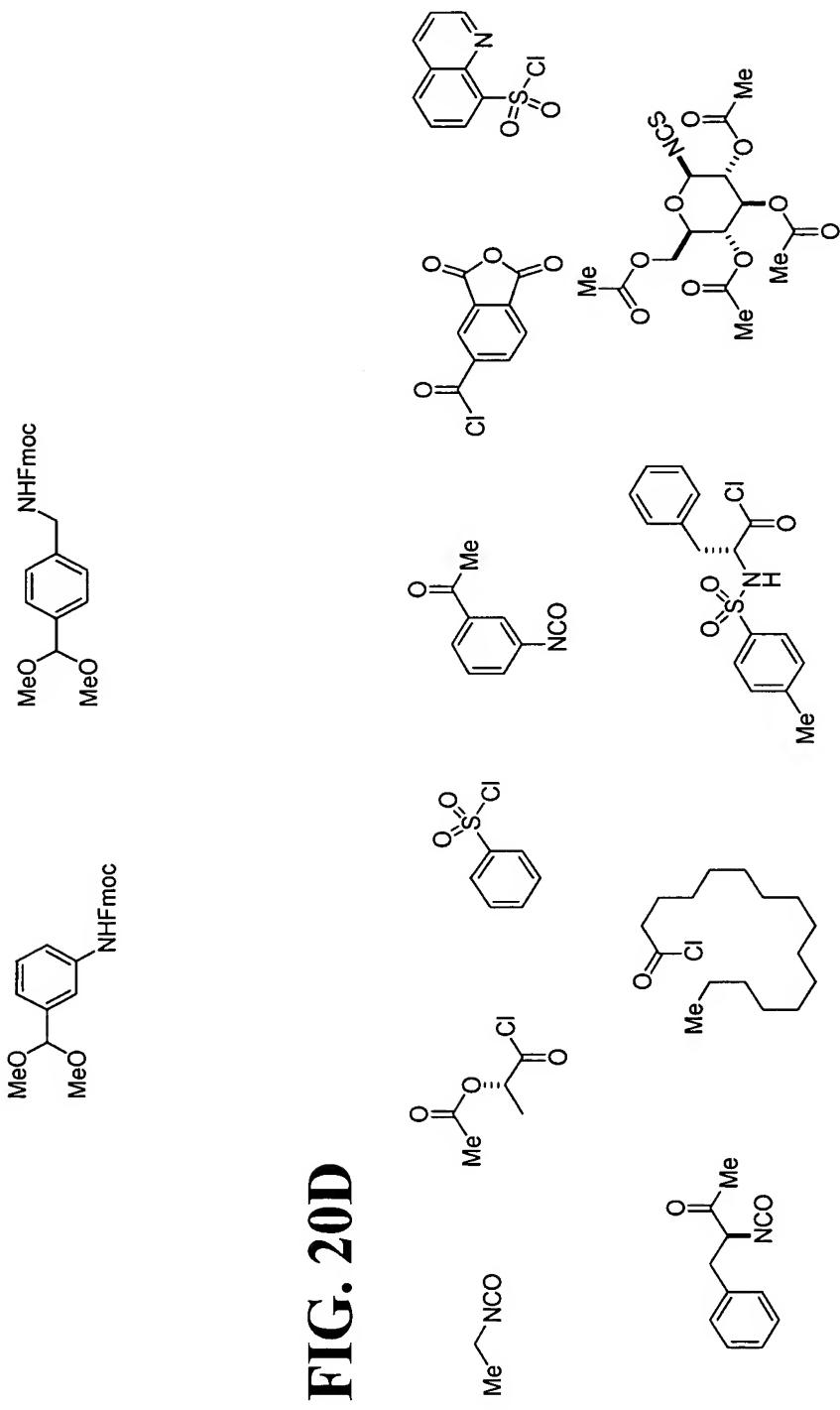
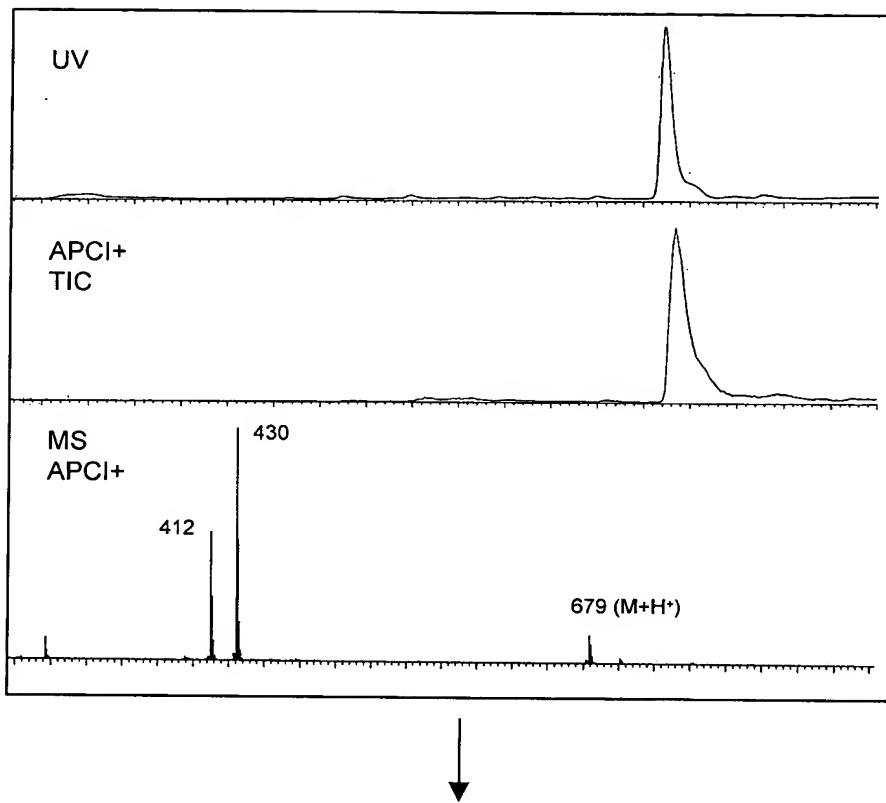


FIG. 20D

FIG. 21A

To FIG. 21B

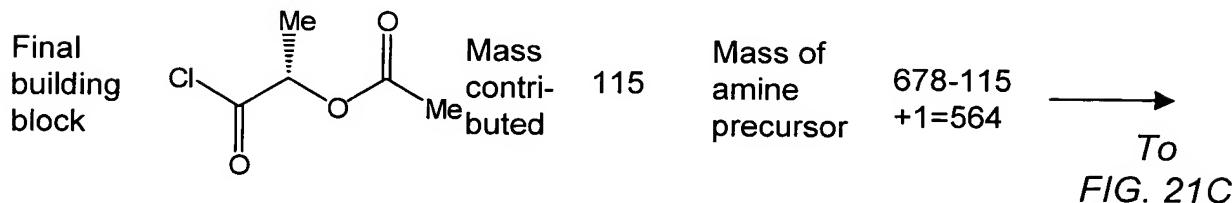
FIG. 21B

FIG. 21C

30 nucleophiles	acetal fragment	3-epoxy alcohols	acetal fragment	3-epoxy alcohols
	103	194 208 270	117	194 208 270
	71	368 382 444	71	382 396 458
	78	375 389 451	78	389 403 465
	87	384 398 460	87	398 412 474
	101	398 412 474	101	412 426 488
	101	398 412 474	101	412 426 488
	111	408 422 484	111	422 436 498
	113	410 424 486	113	424 438 500
	116	413 427 489	116	427 441 503
	118	415 429 491	118	429 443 505
	125	422 436 498	125	436 450 512
	126	423 437 499	126	437 451 513
	127	424 438 500	127	438 452 514
	132	429 443 505	132	443 457 519
	136	433 447 509	136	447 461 523
	136	433 447 509	136	447 461 523
	143	440 454 516	143	454 468 530
	154	451 465 527	154	465 479 541
	155	452 466 528	155	466 480 542
	164	461 475 537	164	475 489 551
	165	462 476 538	165	476 490 552
	167	464 478 540	167	478 492 554
	167	464 478 540	167	478 492 554
	193	490 504 566	193	504 518 580
	194	491 505 567	194	505 519 581
	211	508 522 584	211	522 536 598
	217	514 528 590	217	528 542 604
	221	518 532 594	221	532 546 608
	231	528 542 604	231	542 556 618
	253	550 564 626	253	564 578 640
	263	560 574 636	263	574 588 650

↓
To
FIG. 21D

FIG. 21D

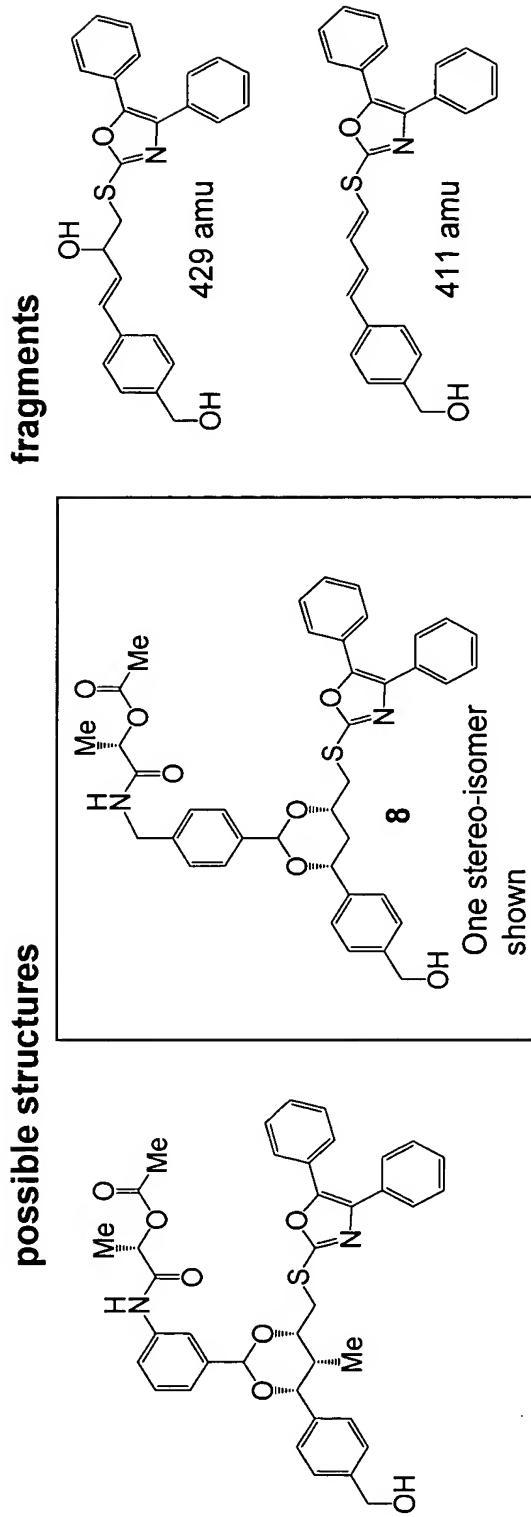


FIG. 21E

To FIG. 21E

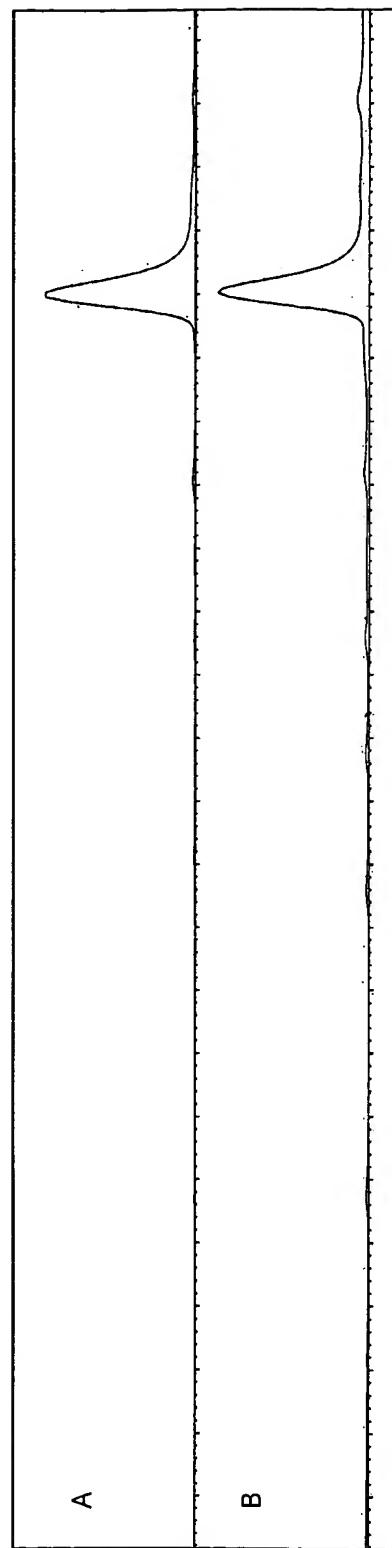


FIG. 22A

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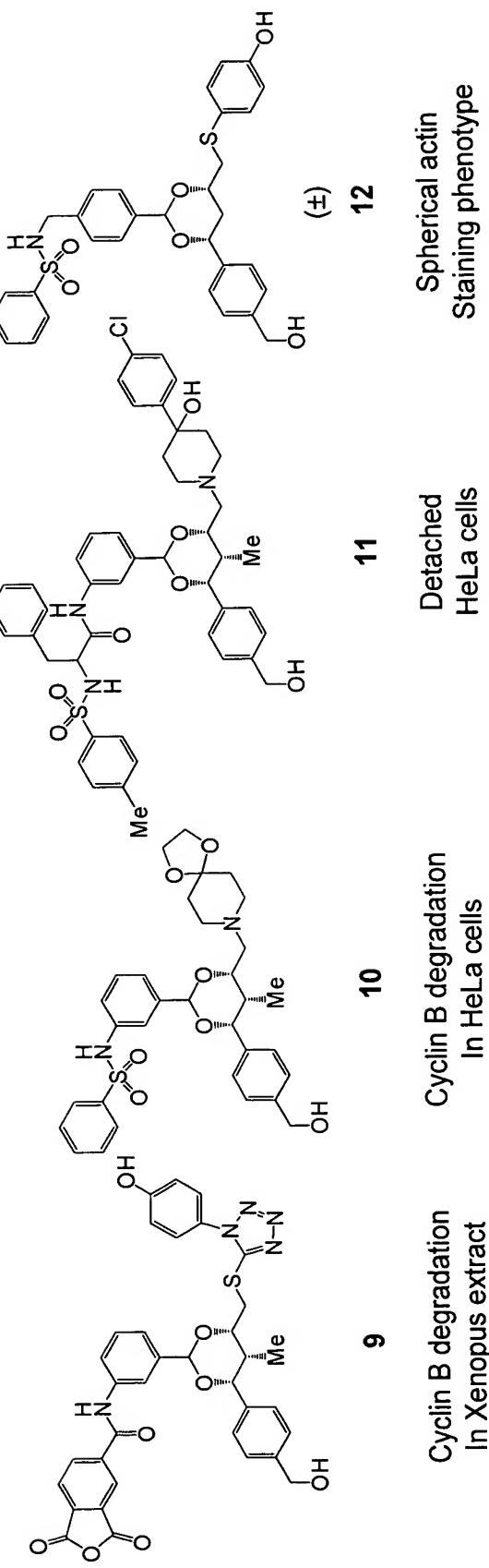
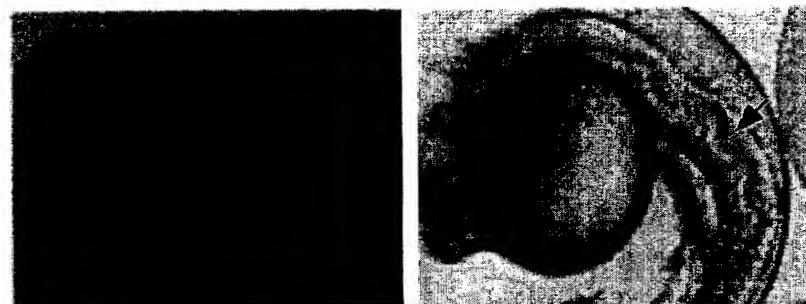


FIG. 22B



No compound

60 μ M
24h

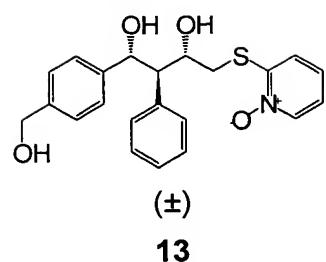
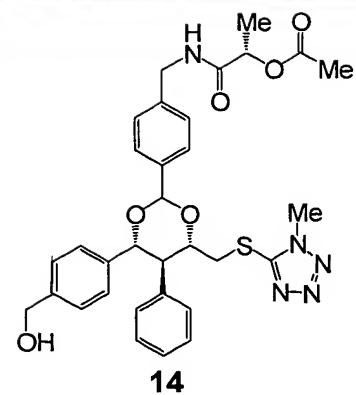
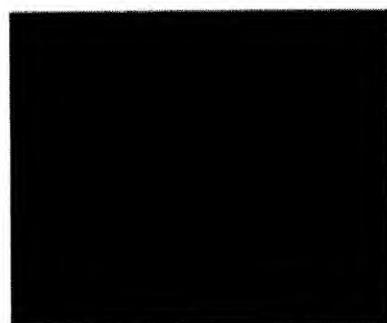


FIG. 22C



One stereoisomer shown

FIG. 23A

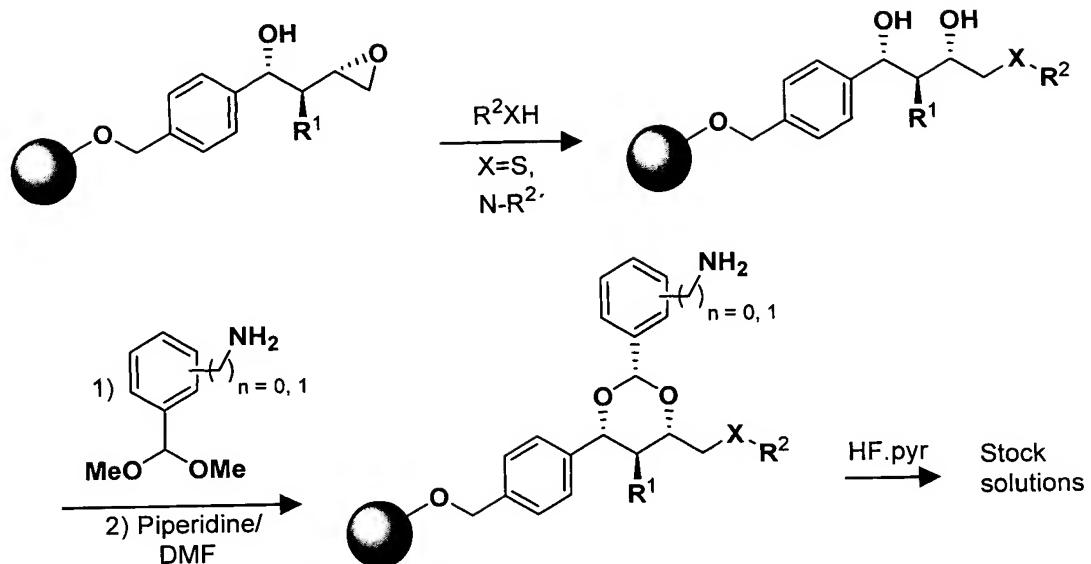


FIG. 23B

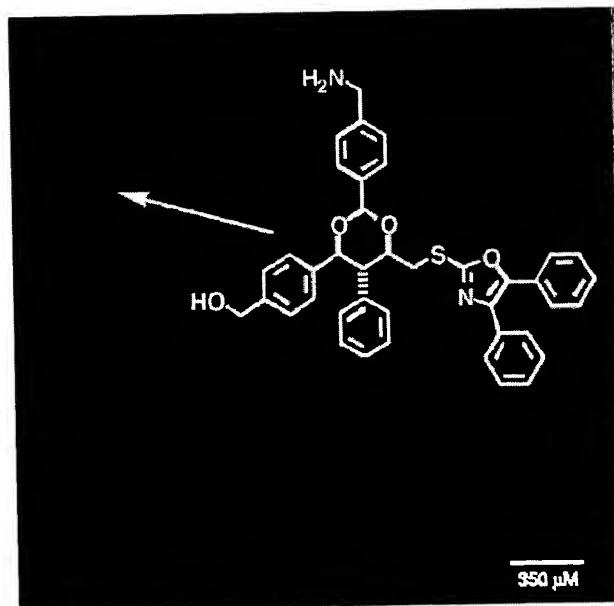


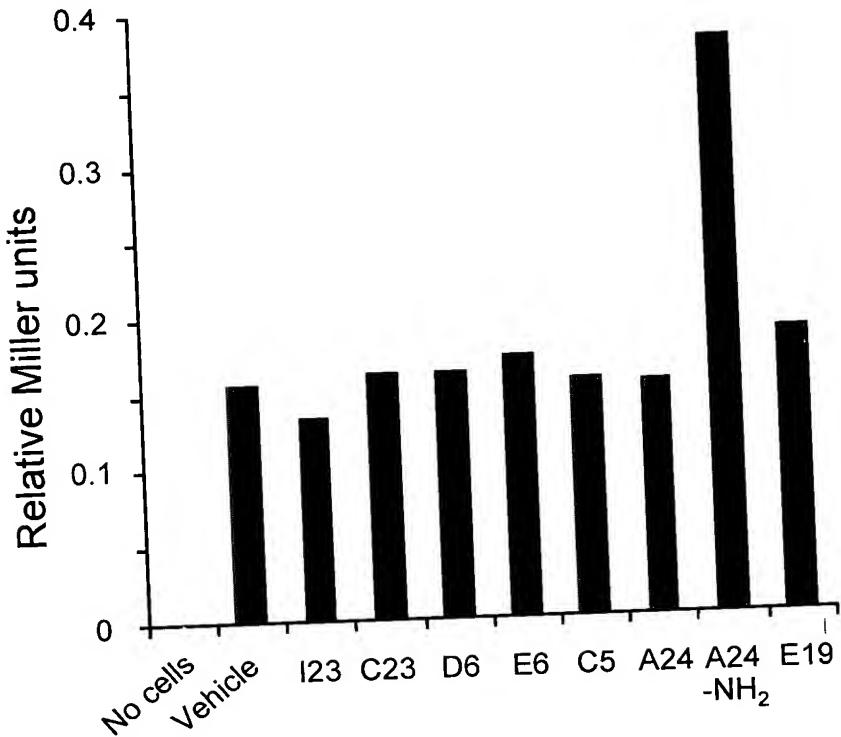
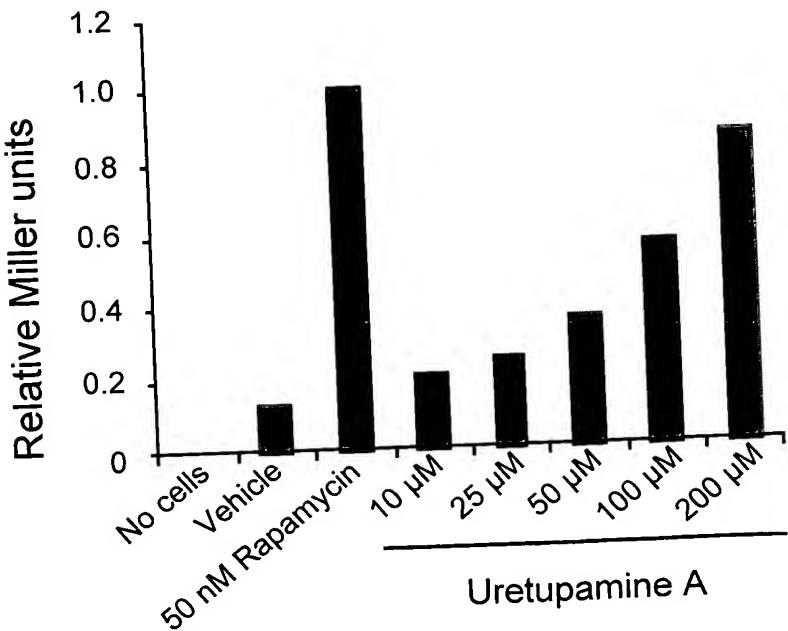
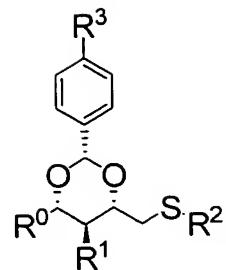
FIG. 24A**FIG. 24B**

FIG. 24C

Uretupamine	R ⁰	R ¹	R ²	R ²	Activity
A	HOCH ₂ -4-Ph	Ph	2-MDPO	CH ₂ NH ₂	56
B	HOCH ₂ -4-Ph	H	2-MDPO	CH ₂ NH ₂	105
C	HOCH ₂ -4-Ph	(β)-CH ₃	2-MDPO	CH ₂ NH ₂	41*
D	HOCH ₂ -4-Ph	H	Ph	CH ₂ NH ₂	7
E	HOCH ₂ -4-Ph	H	2-MBO	CH ₂ NH ₂	10
F	HOCH ₂ -4-Ph	H	2-MDPO	H	14
G	HOCH ₂ -4-Ph	H	2-MDPO	CH ₂ NHAc	16
H		H	2-MDPO	CH ₂ NH ₂	13

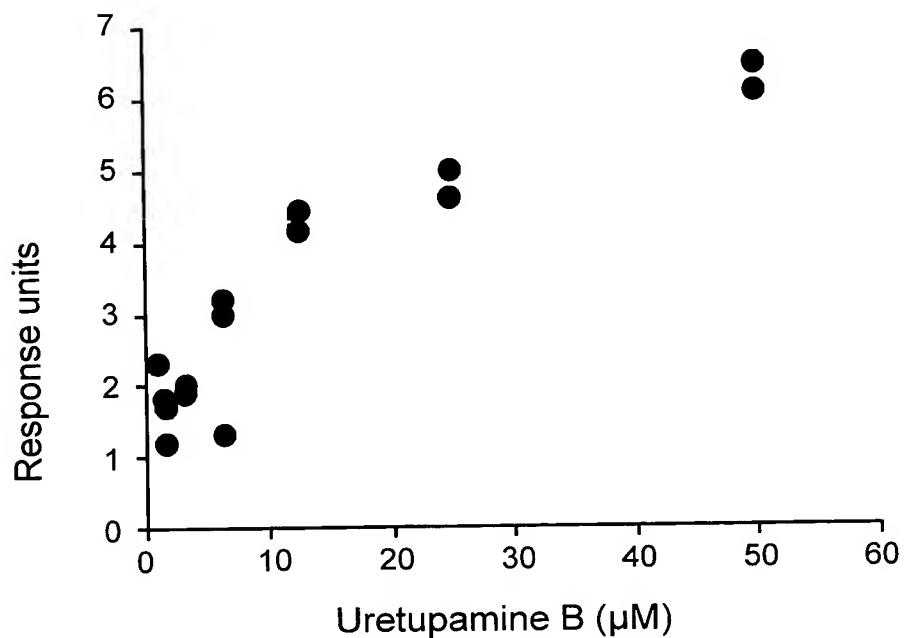
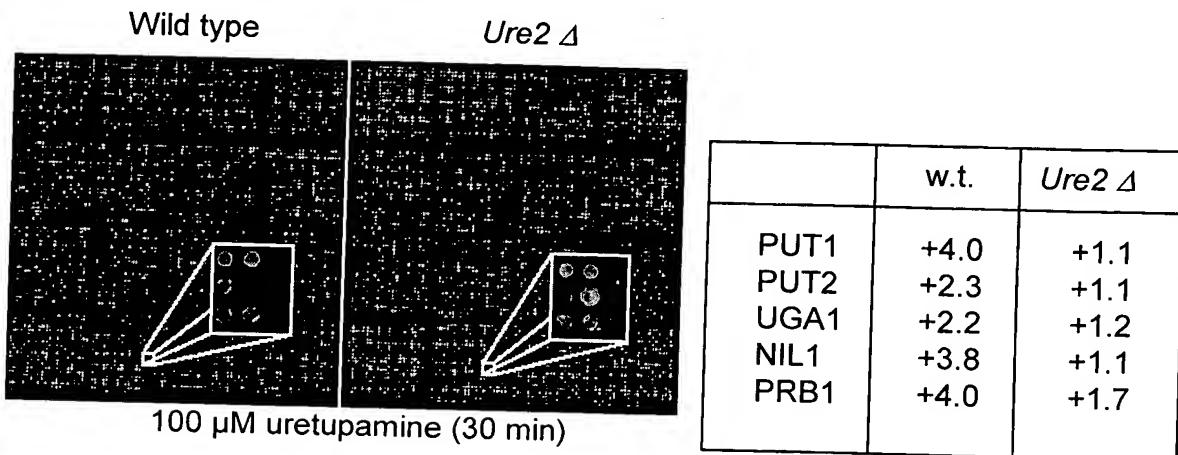
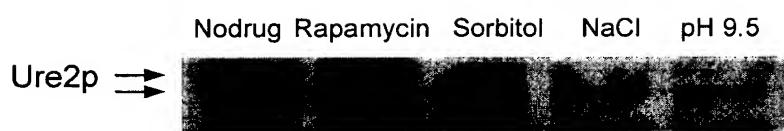
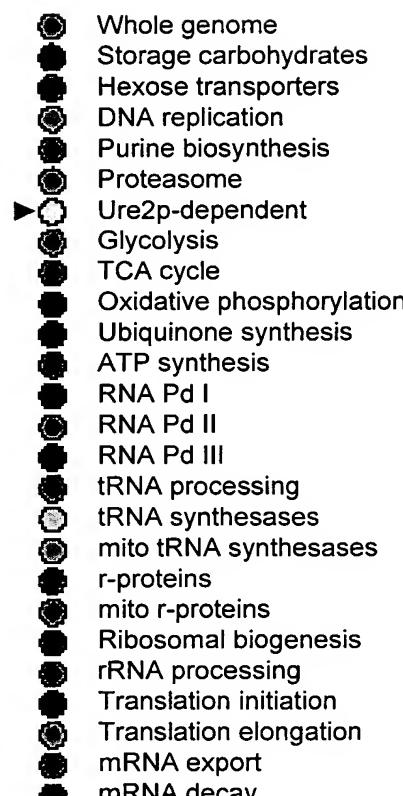
FIG. 24D

FIG. 25A**FIG. 25B**

Gene sets	w.t.	<i>gln3</i> Δ	<i>nil1</i> Δ	<i>ure2</i> Δ
GAP1, MEP2, DAL5, BAT2, AGP1	+1.1	+1.1	-1.0	-1.0
PUT1, PUT2, UGA1, NIL1, PRB1	+2.3	+2.5	+1.6	+1.2

FIG. 25C

Gene sets	w.t.	<i>gln3</i> Δ	<i>nil1</i> Δ	<i>ure2</i> Δ
Whole genome	100%	89%	56%	52%
URE2-dependent genes	100%	115%	51%	59%

FIG. 26A**FIG. 26B****FIG. 26C**

Correlated Uncorrelated Anticorrelated

FIG. 26D

	Ethanol	Acetate
PUT1	+11.5	> +10.0
PUT2	+2.8	+1.6
UGA1	+4.7	+3.3
NIL1	+2.6	+2.5
PRB1	+2.3	+1.4
GAP1	+3.3	-9.0
DAL1	+1.7	-4.8
DAL2	+3.1	-1.5
DAL3	+2.1	< -10.0
CAR1	+2.6	-1.4

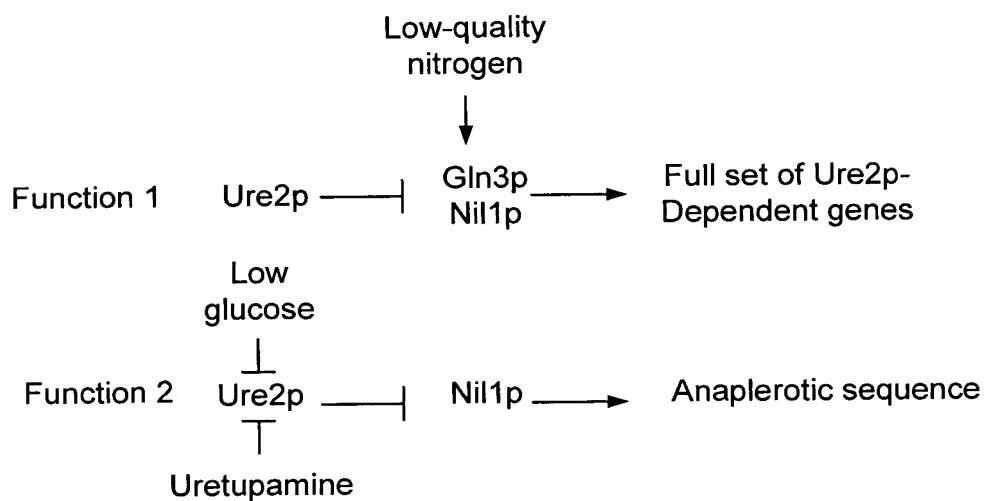
FIG. 26E

FIG. 27A

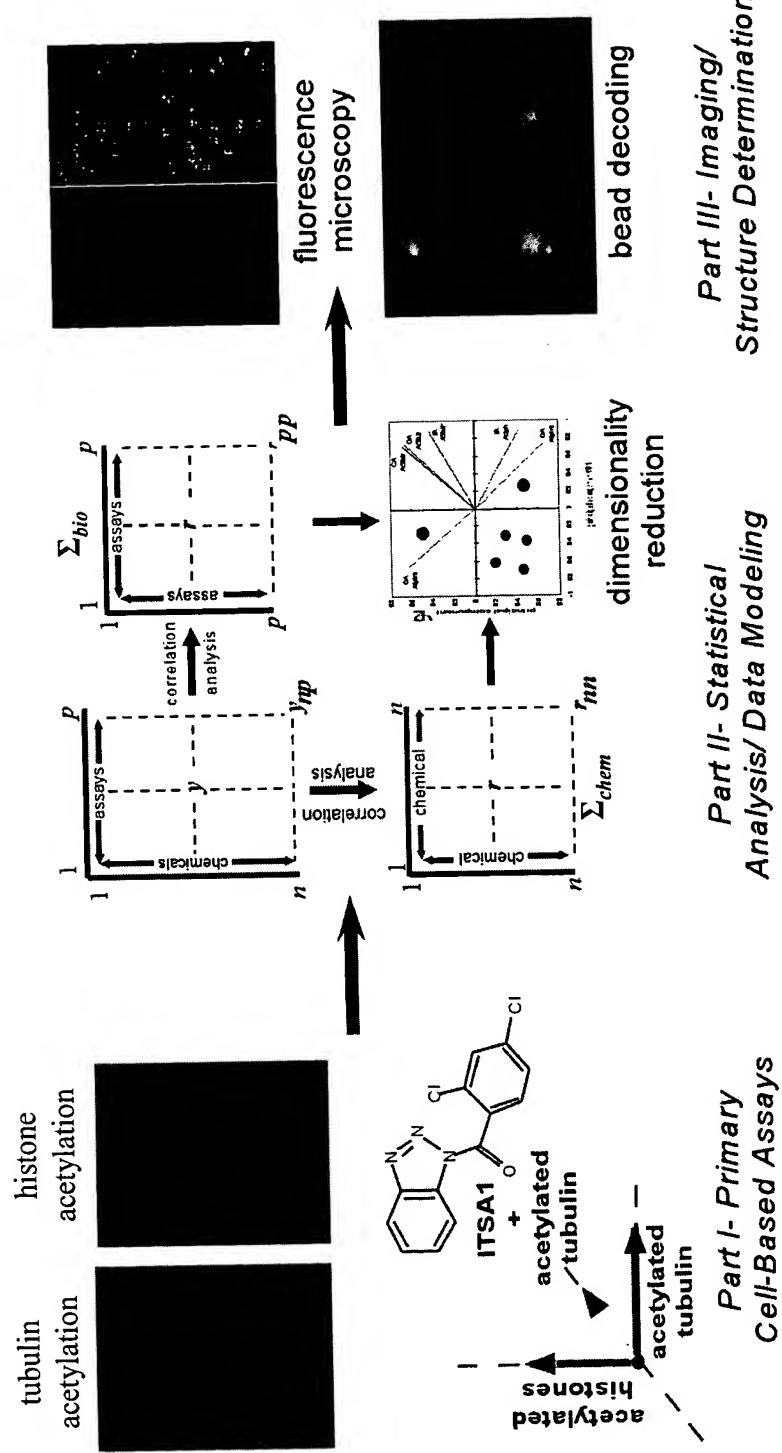
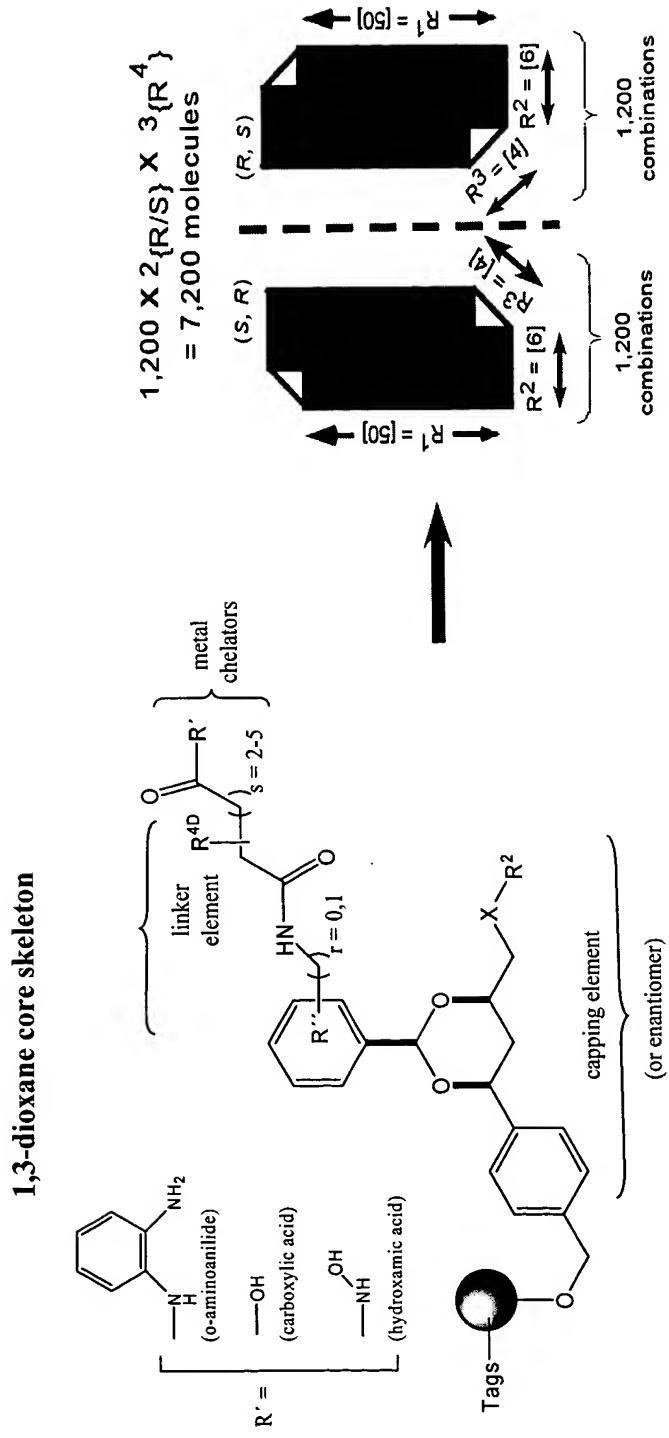


FIG. 27B



Biasing elements in diversity-oriented synthesis

FIG. 27C

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	Assay	Abbreviation	Compounds screened in duplicate
1.	Acetylated tubulin	AcTubulin	7,392
2.	Acetylated tubulin + ITSA1 (chemical genetic modifier)	ITSA1+AcTubulin	2,464 hydroxamic acids
3.	Acetylated lysine	AcLysine	7,392
4.	Acetylated histone H3	AcHistH3	2,464 hydroxamic acids
5.	Acetylated histone H4	AcHistH4	2,464 hydroxamic acids

Table 1. Summary of chemical genetic screens

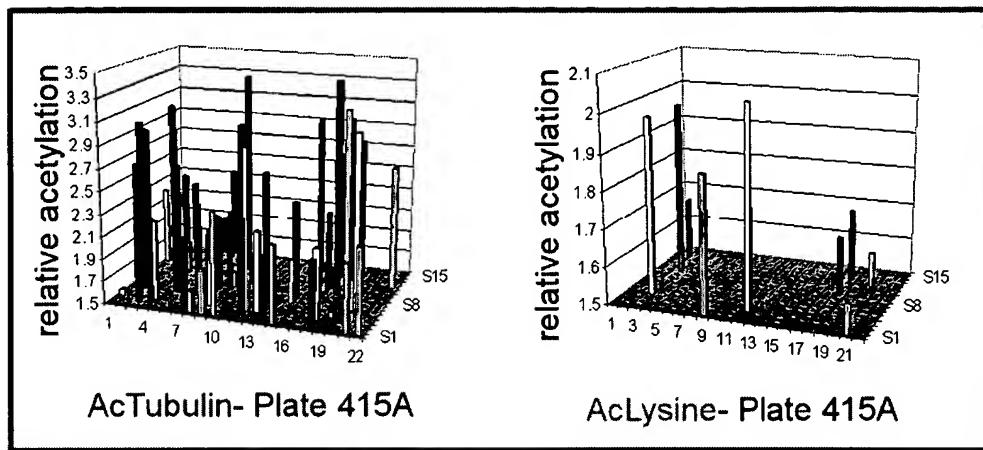
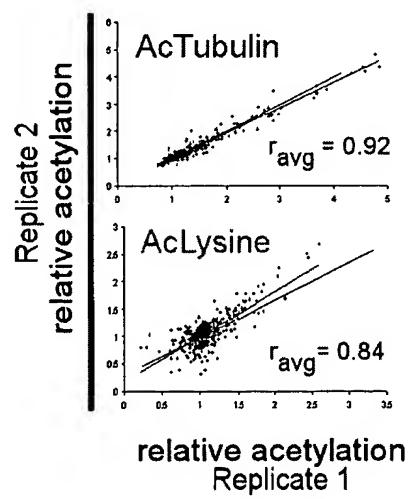
FIG. 28A**FIG. 28B**

FIG. 28C

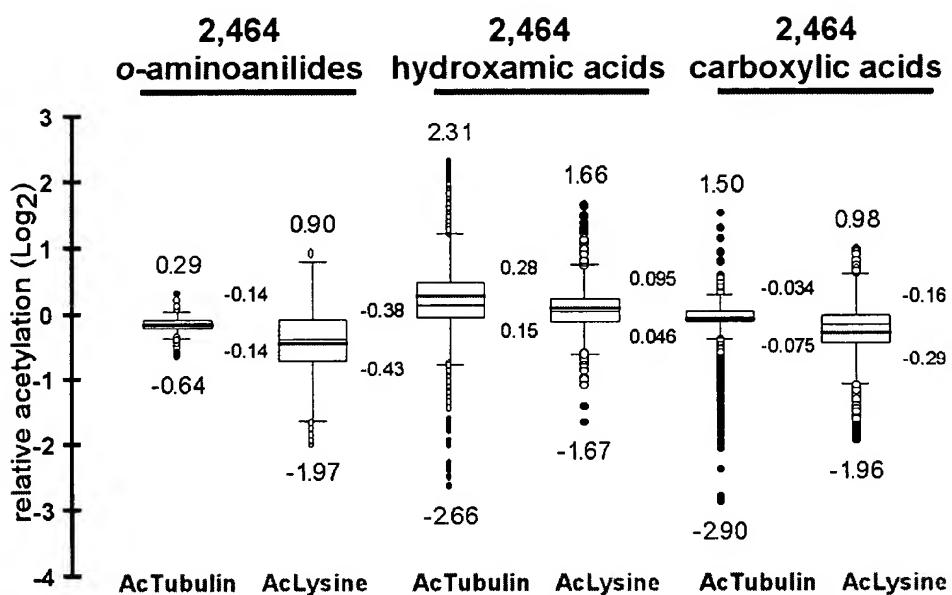


FIG. 28D

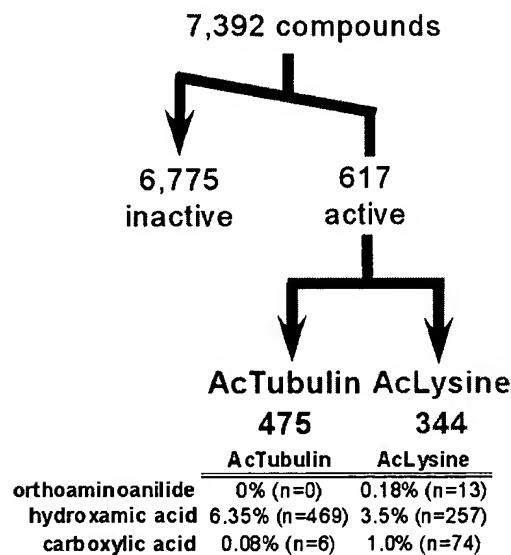


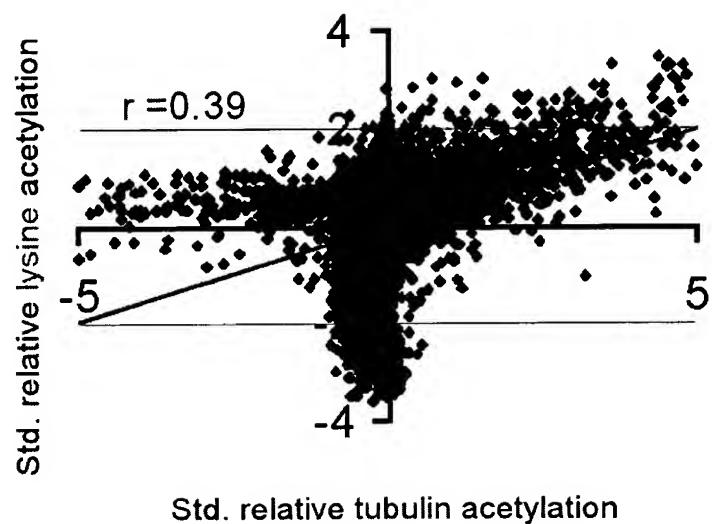
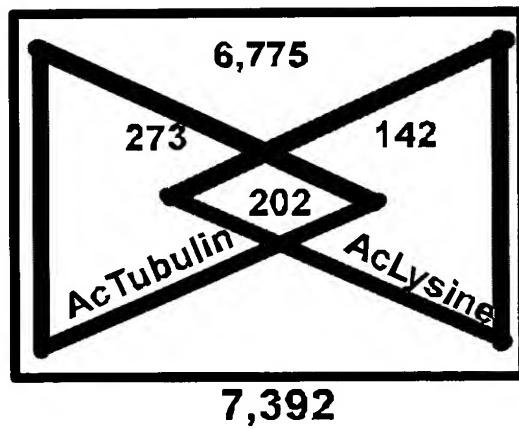
FIG. 29A**FIG. 29B**

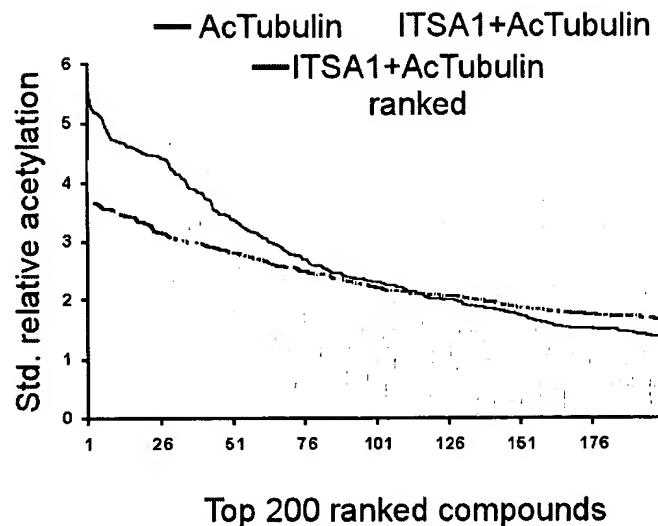
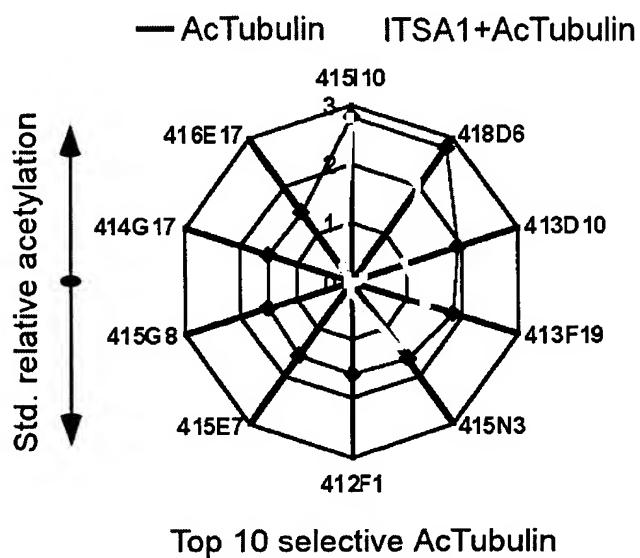
FIG. 29C**FIG. 29D**

FIG. 30A

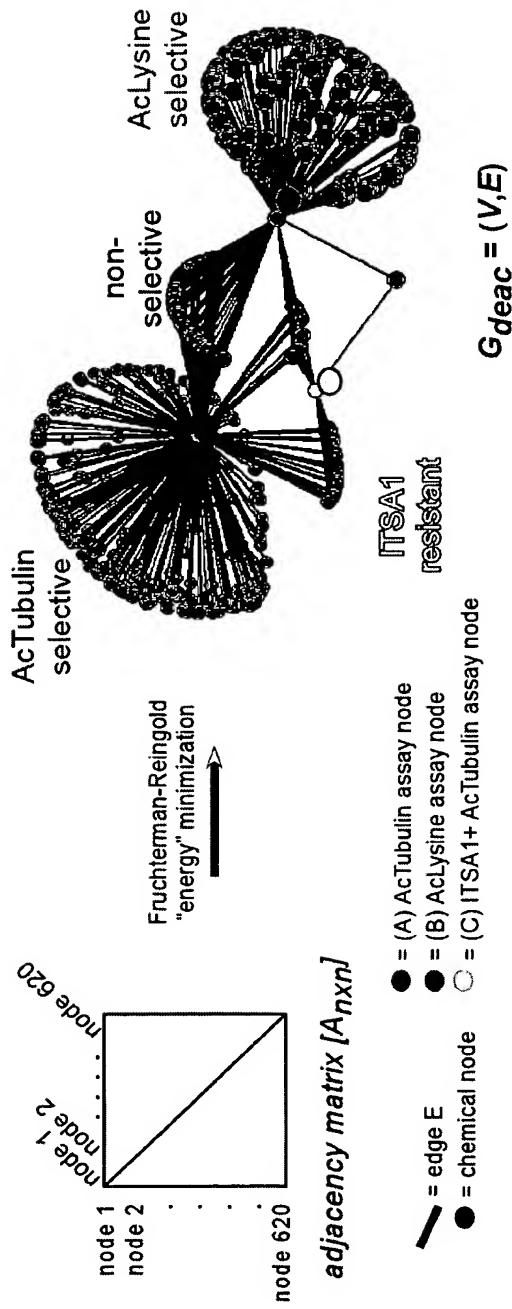


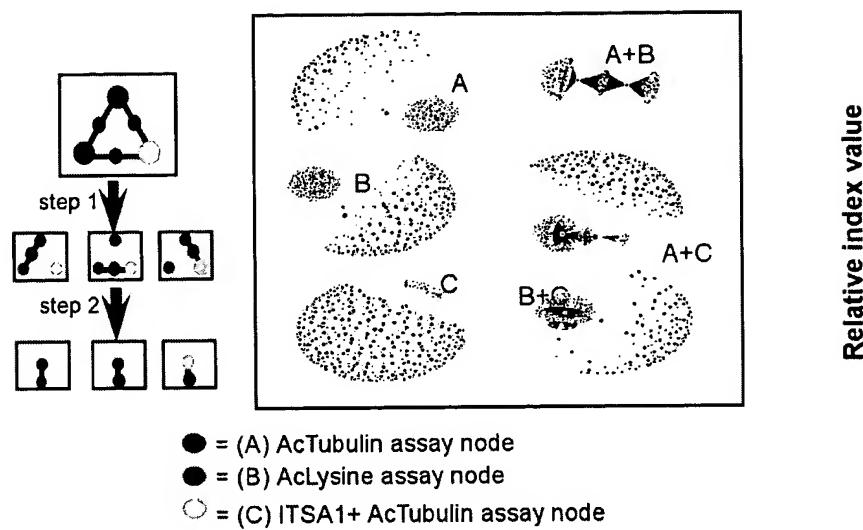
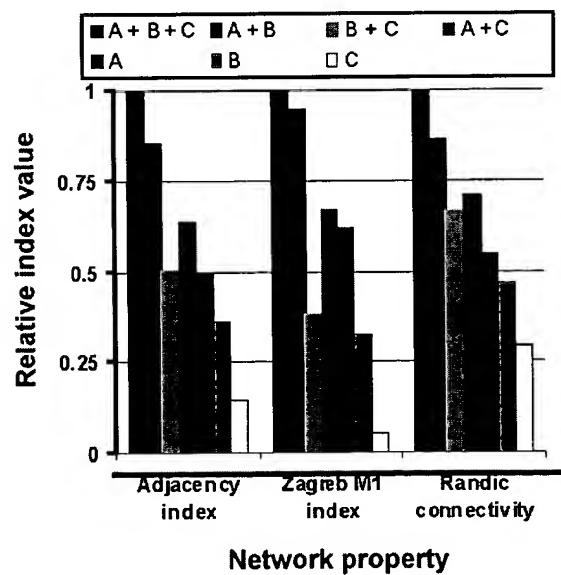
FIG. 30B**FIG. 30C**

FIG. 31

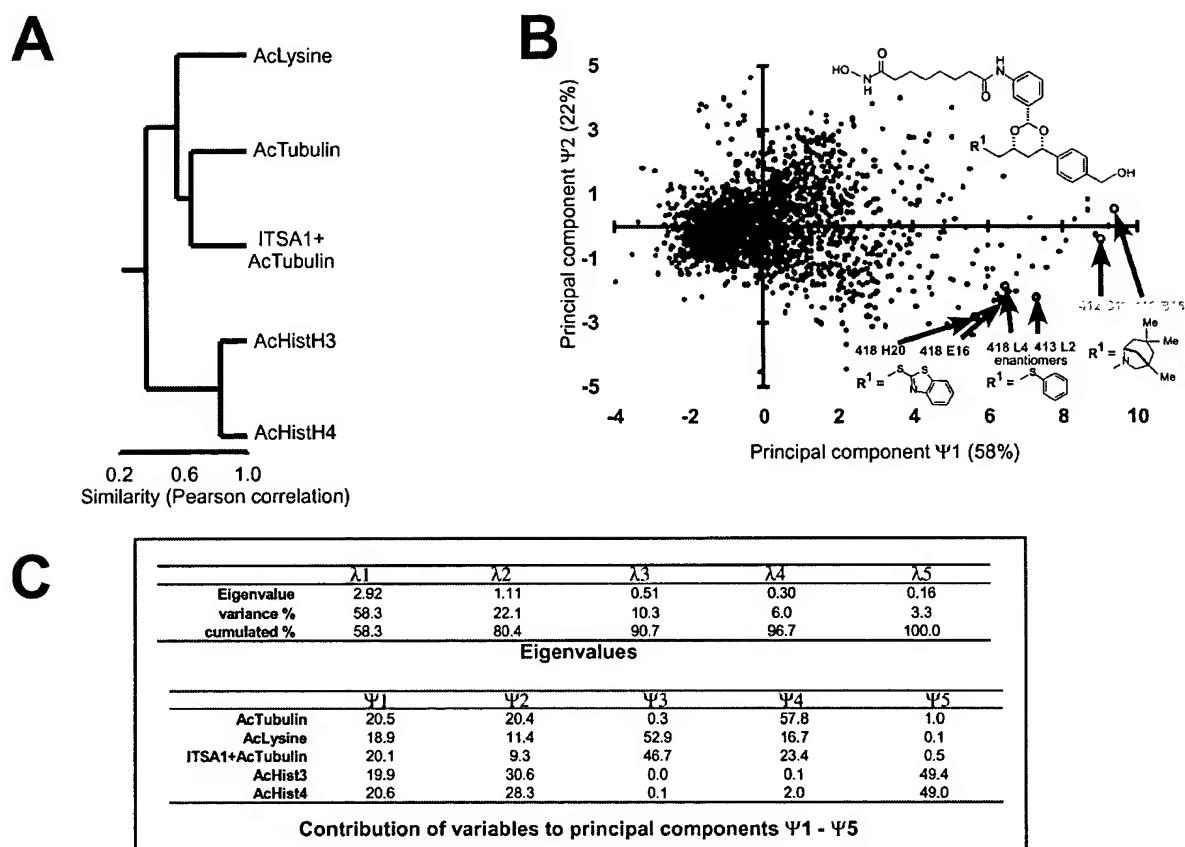


FIG. 32

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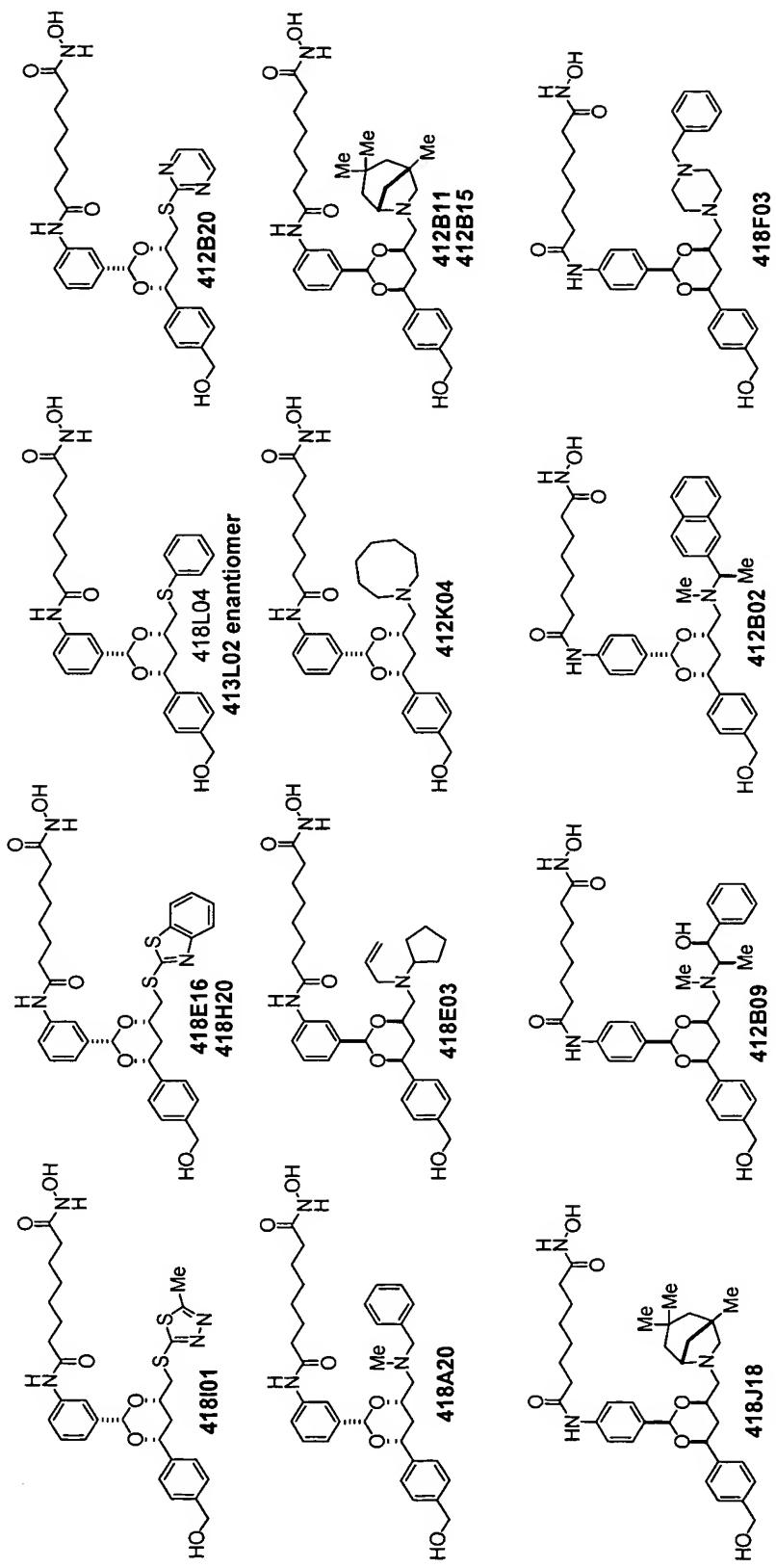


FIG. 33A

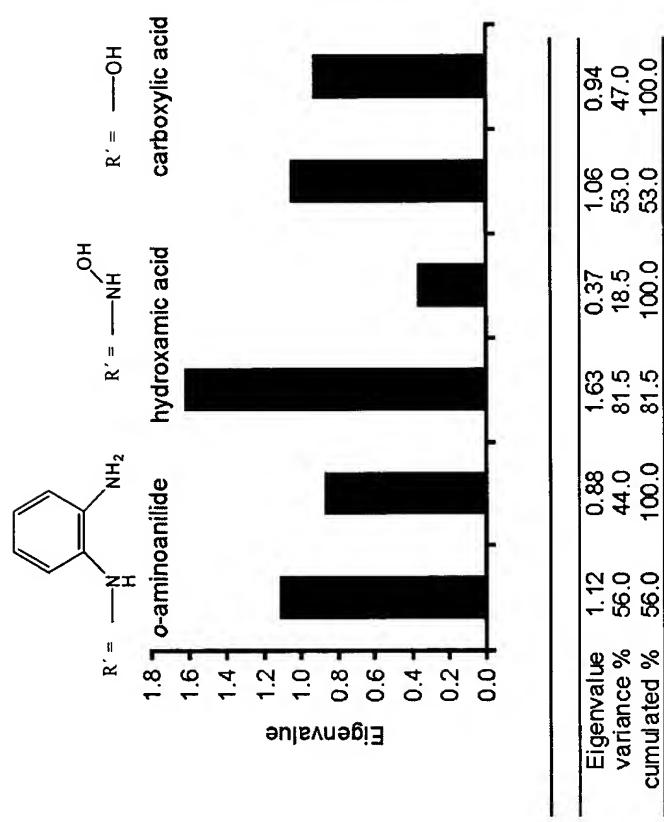


FIG. 33B

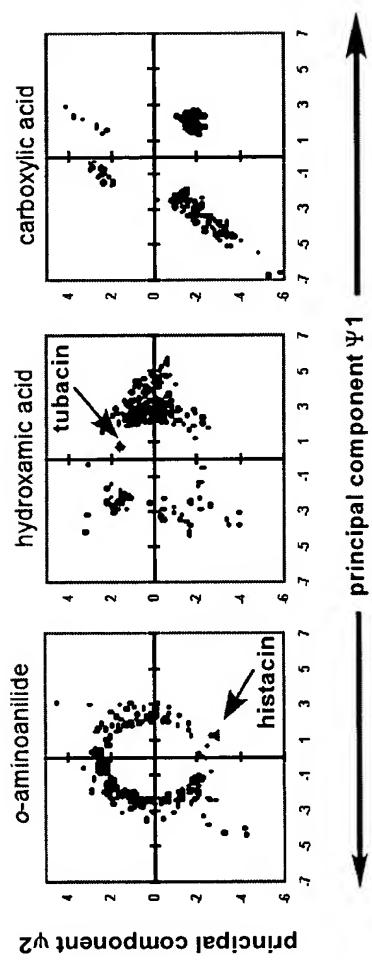


FIG. 33C

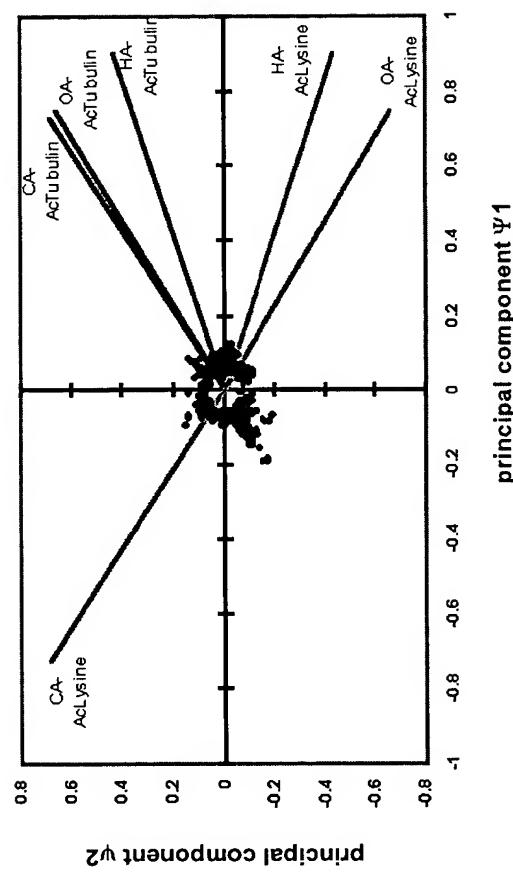


FIG. 34A

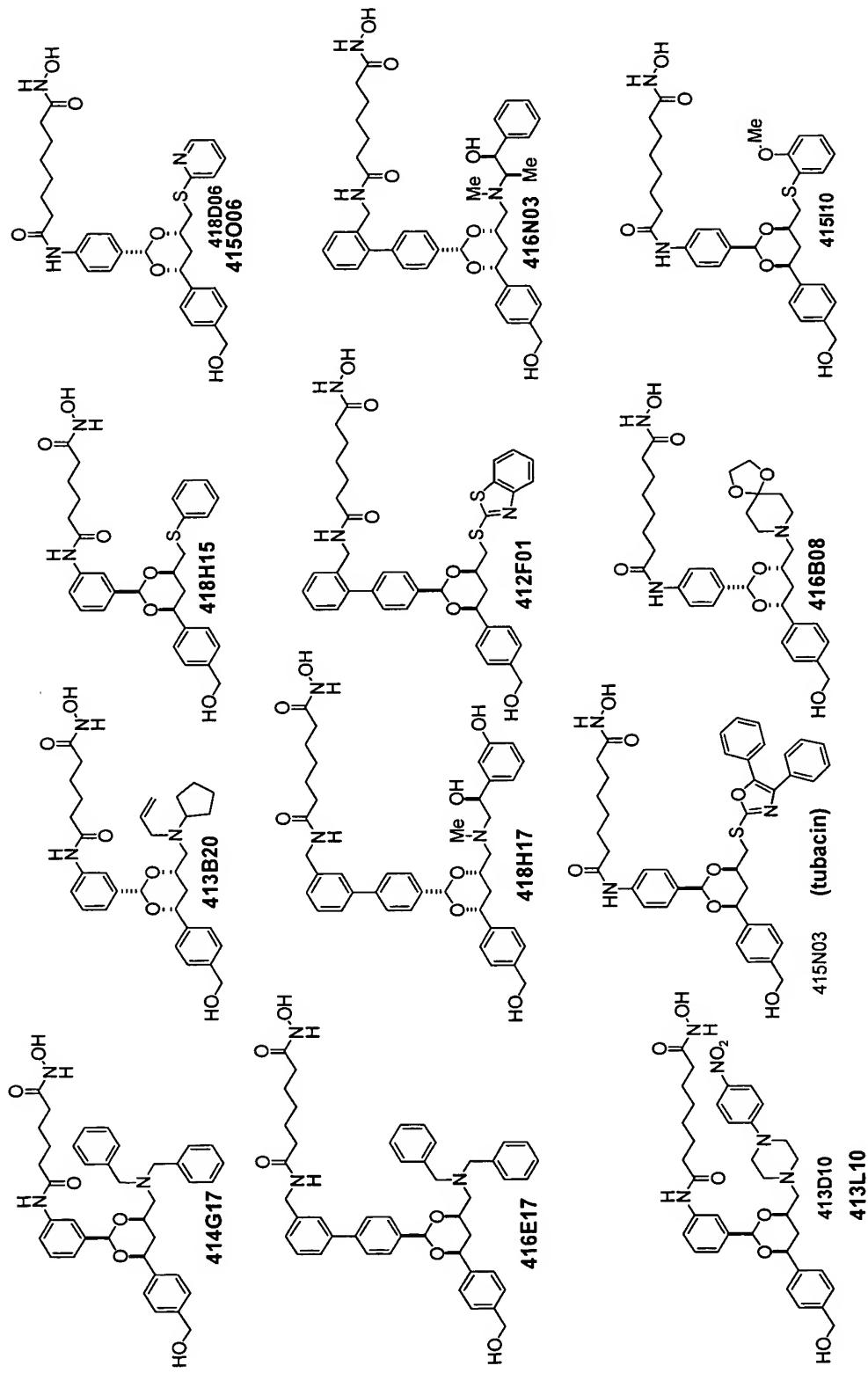


FIG. 34B

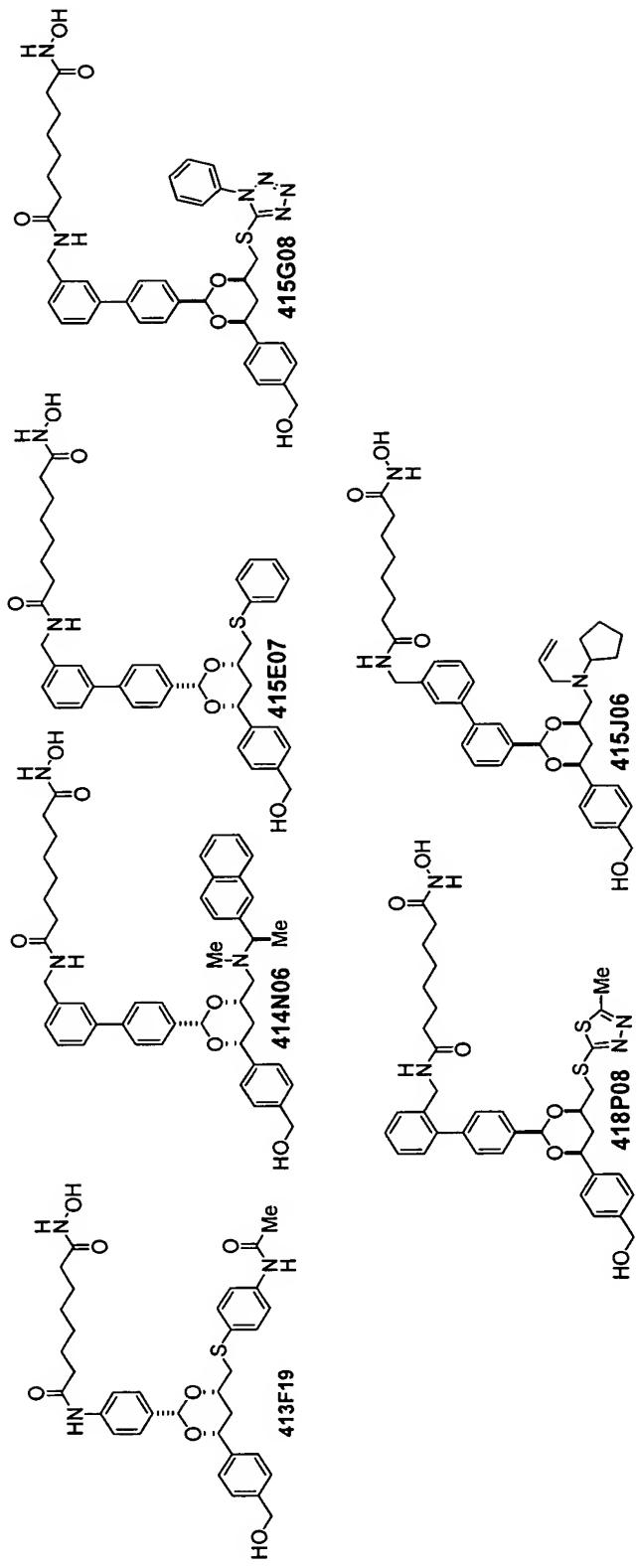


FIG. 35A

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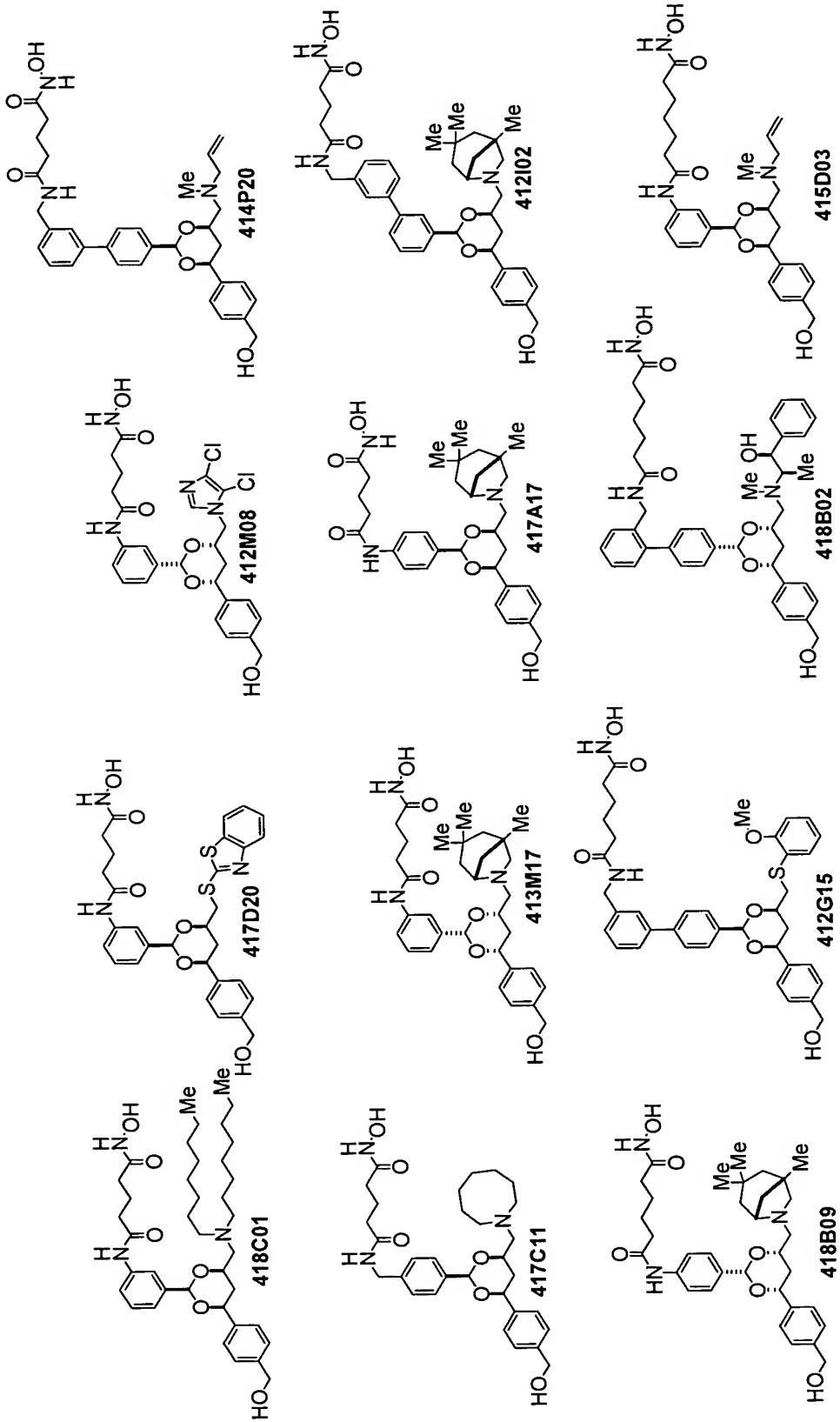


FIG. 35B

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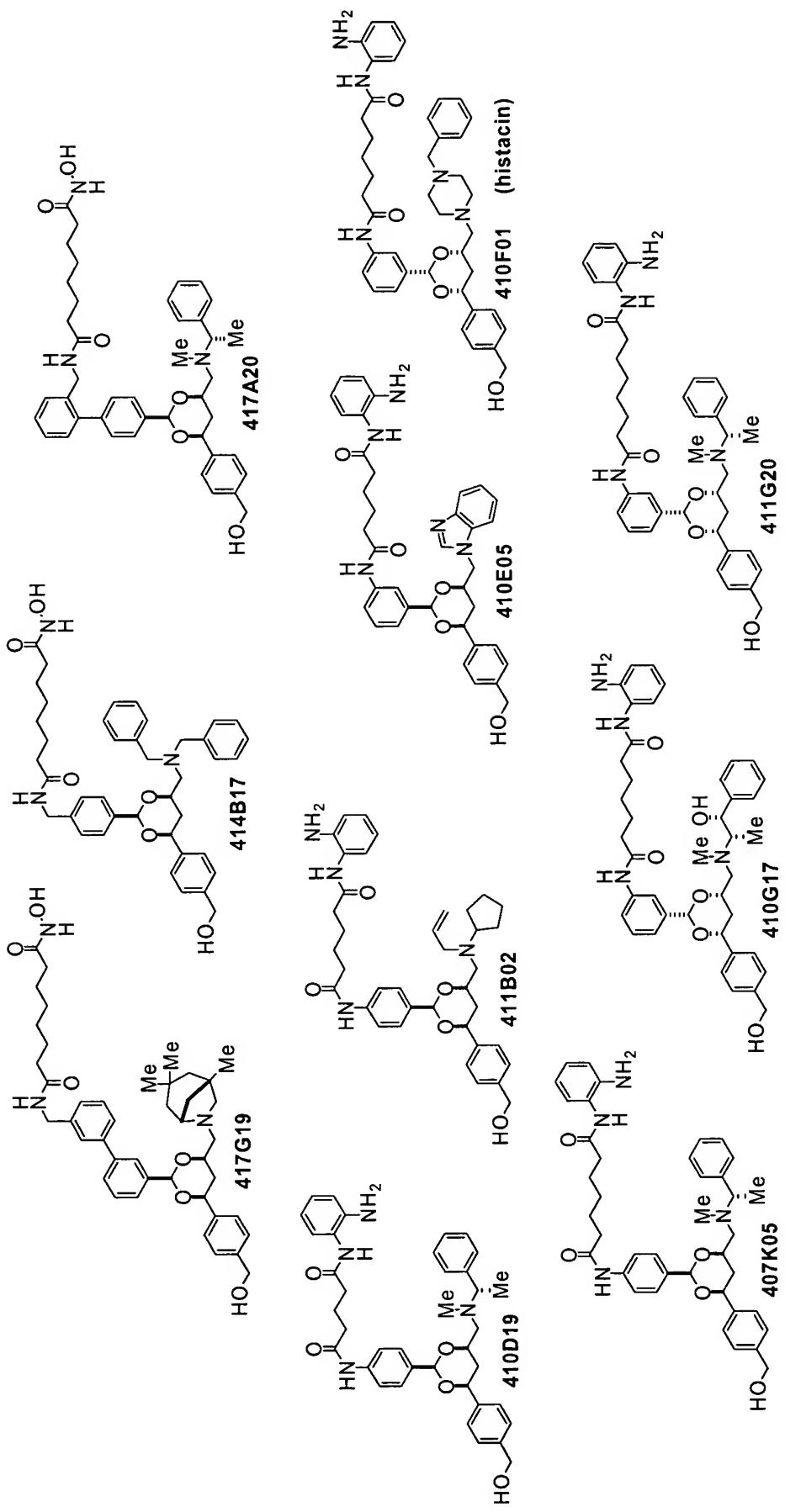


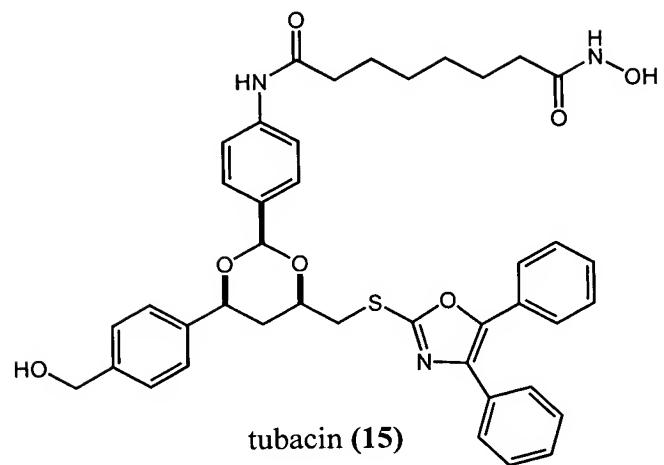
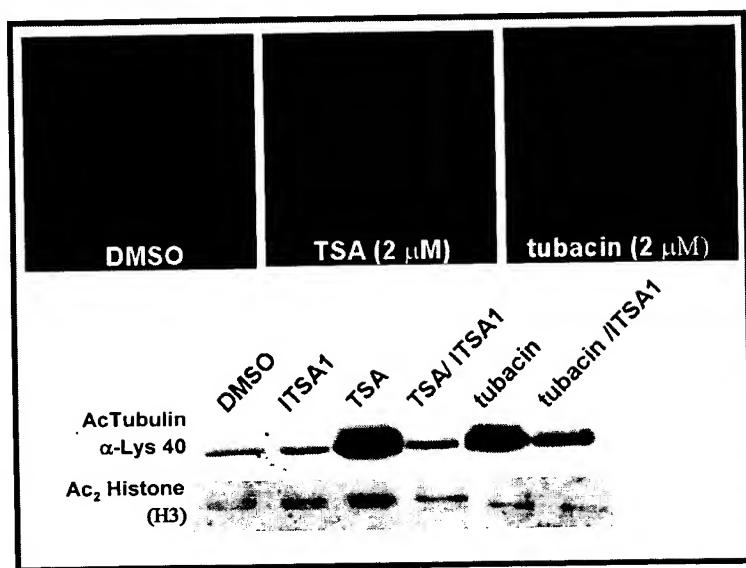
FIG. 36A**FIG. 36B**

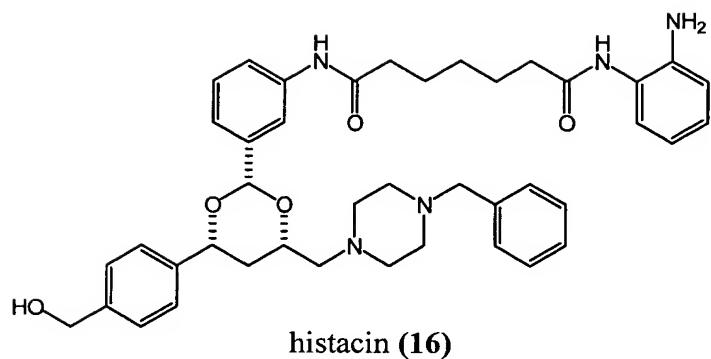
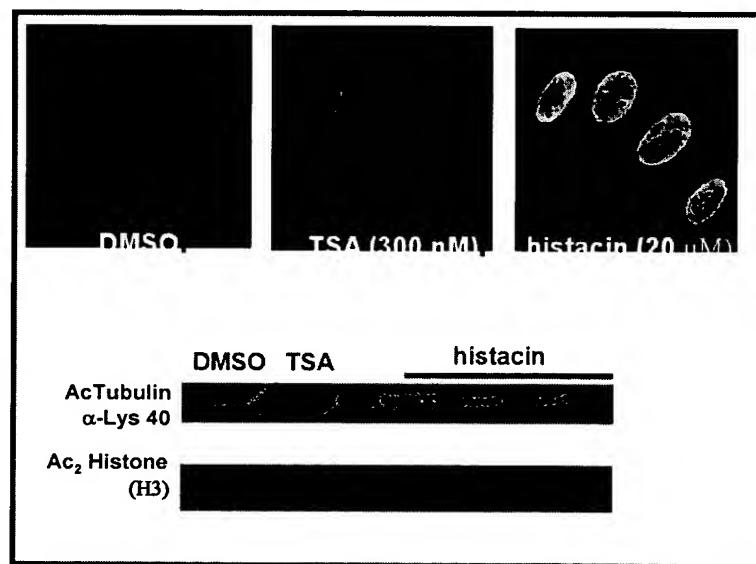
FIG. 36C**FIG. 36D**

FIG. 36E

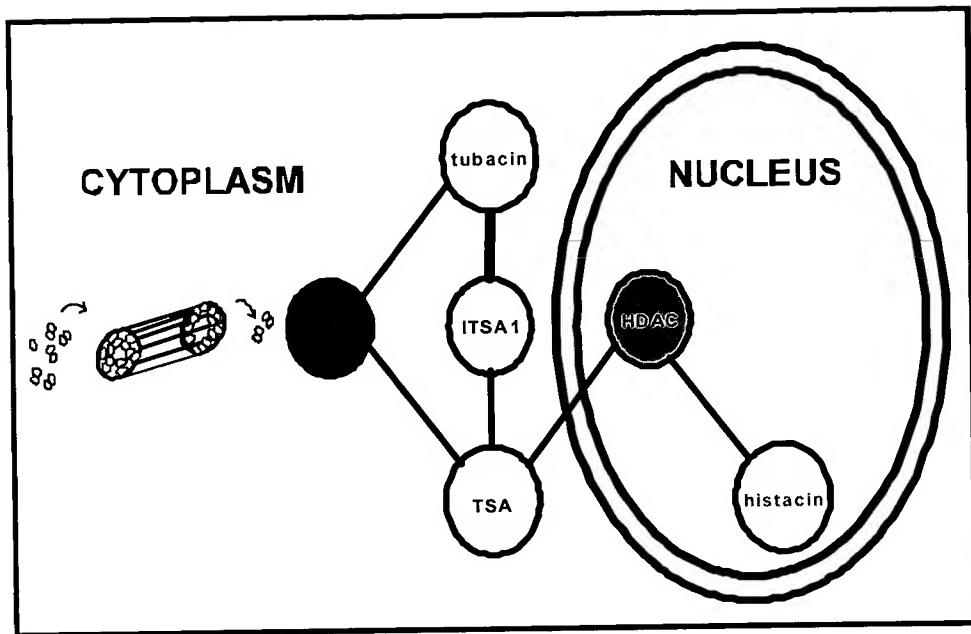
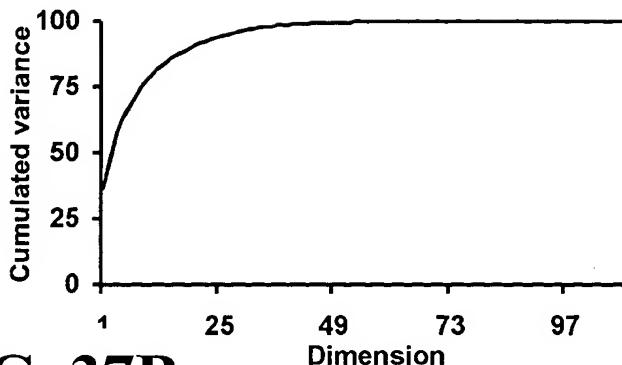


FIG. 37A**FIG. 37B**

	F1	F2	F3	F4	F5
Eigenvalue	40.5	9.7	8.6	6.5	5.2
variance %	36.1	8.6	7.7	5.8	4.6
cumulated %	36.1	44.8	52.5	58.3	62.9

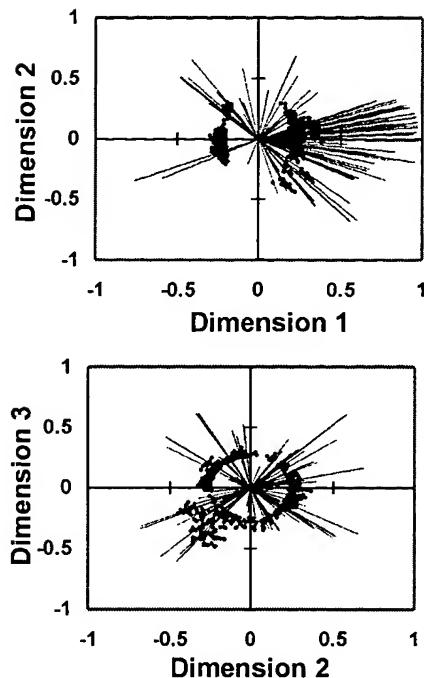
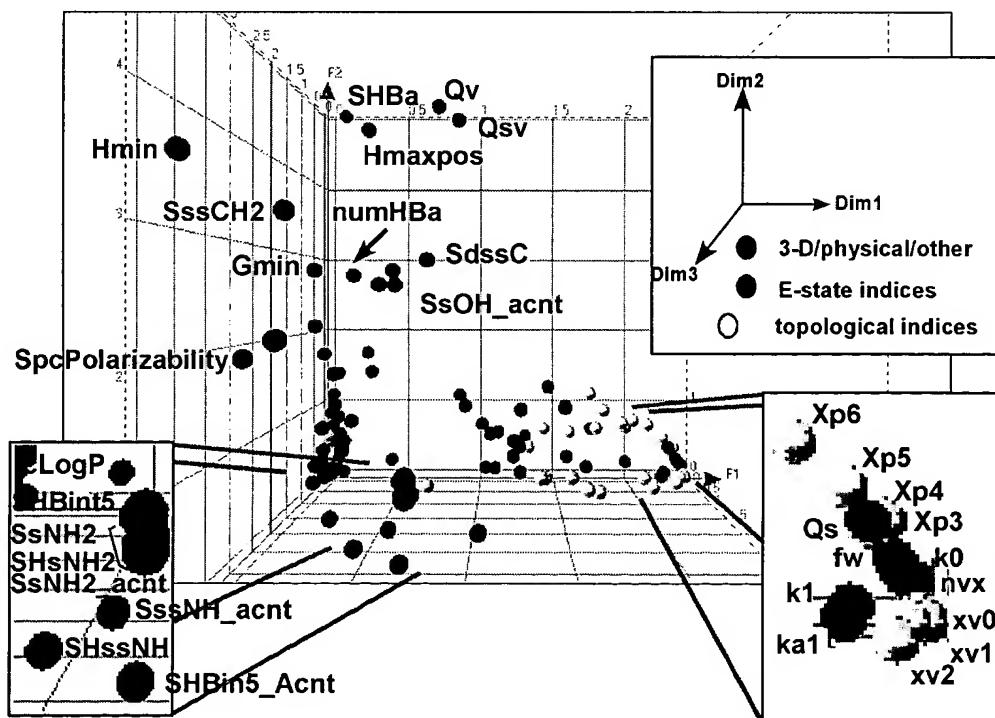
FIG. 37C**FIG. 37D**

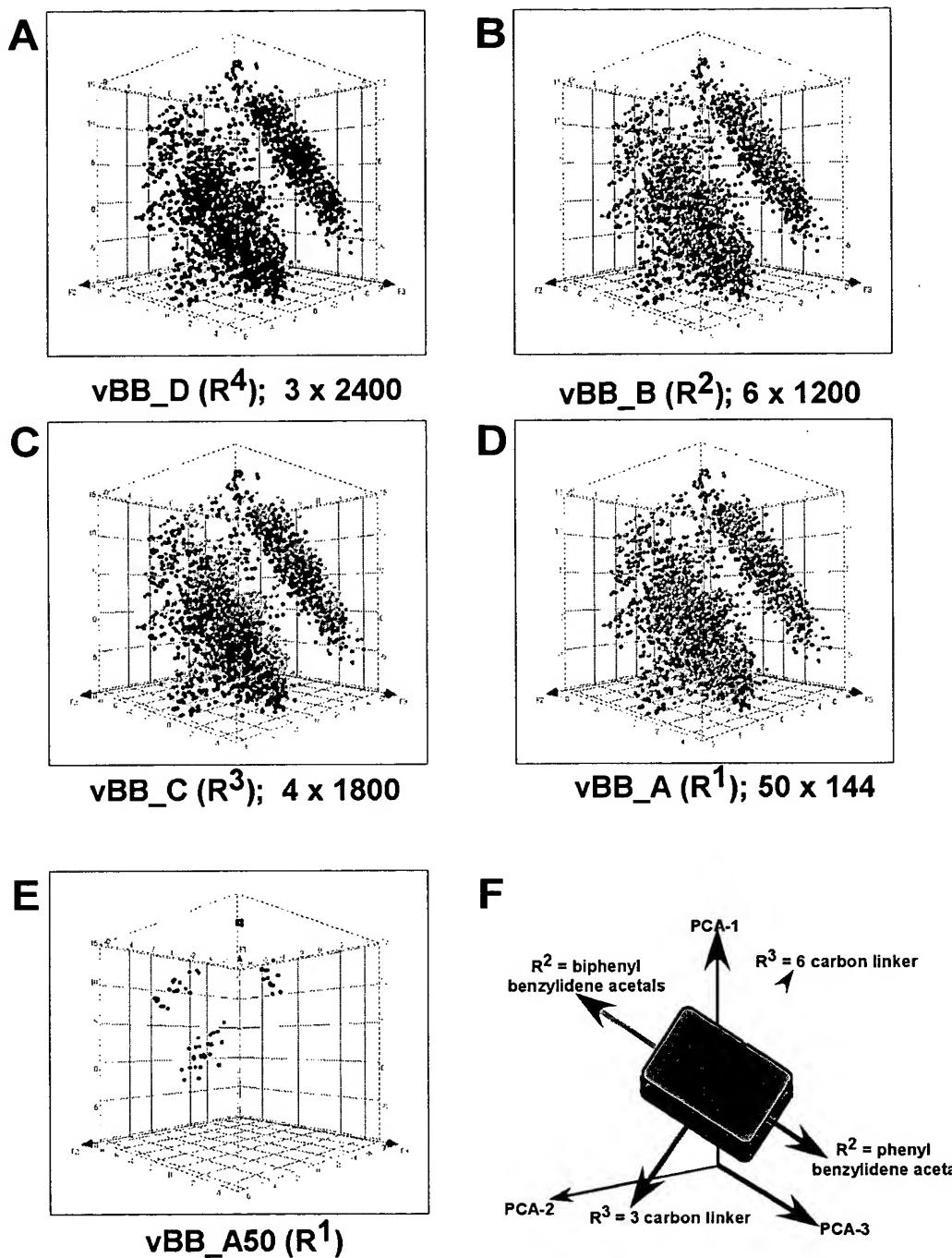
FIG. 38

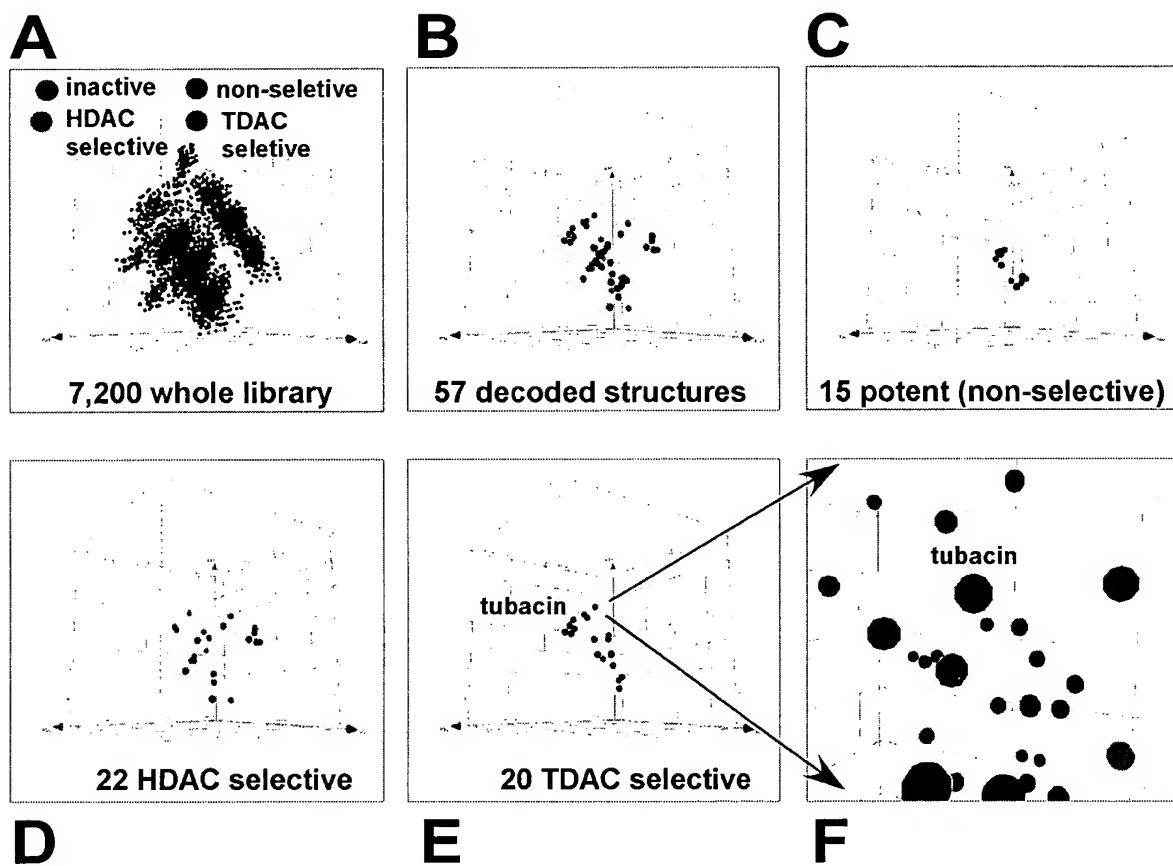
FIG. 39

FIG. 40

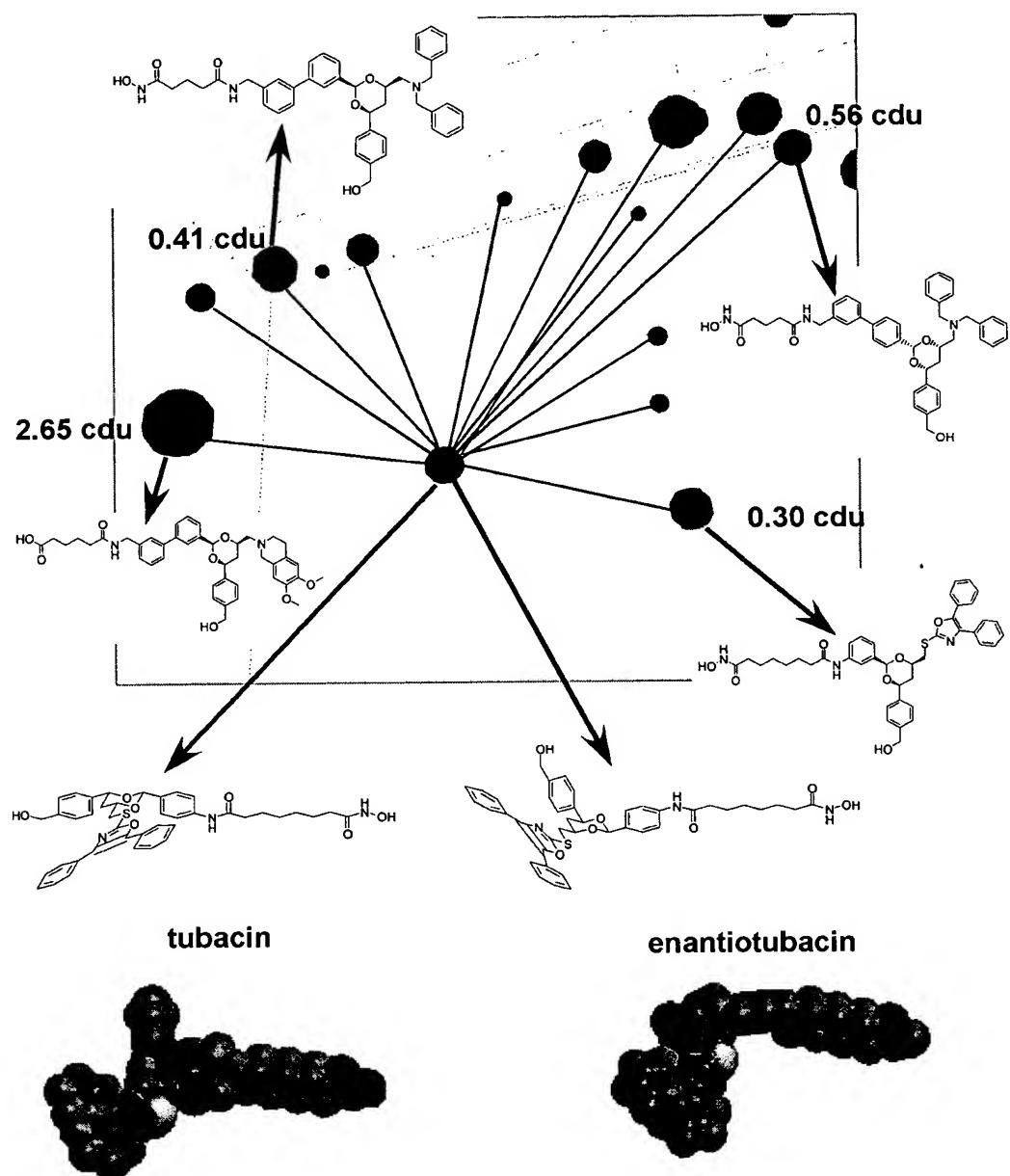


FIG. 41A

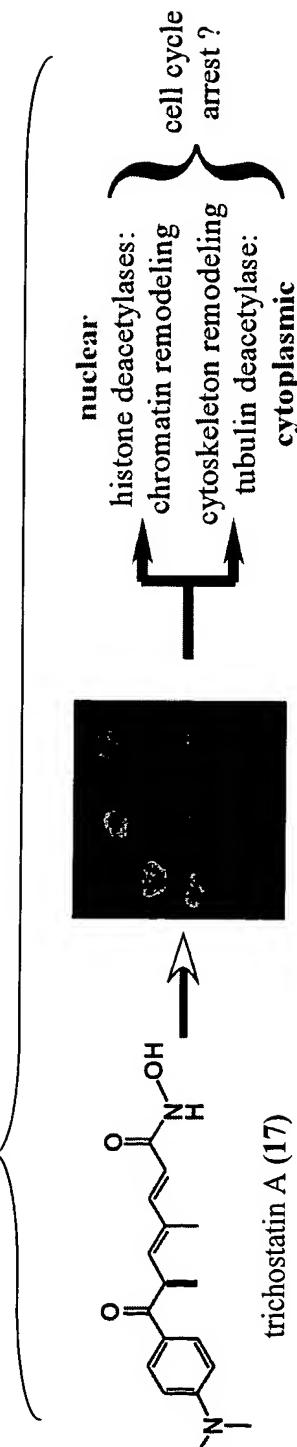


FIG. 41B

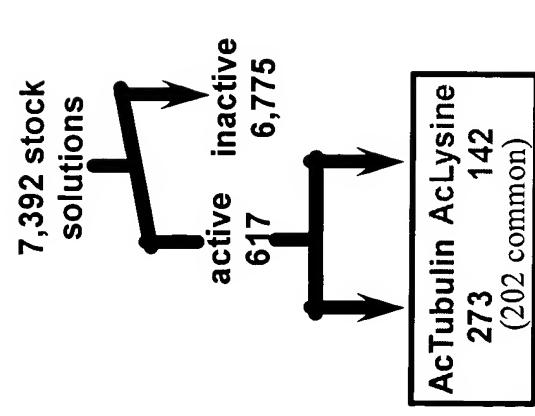


FIG. 41C

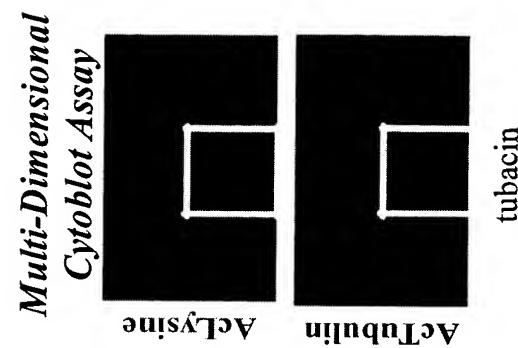


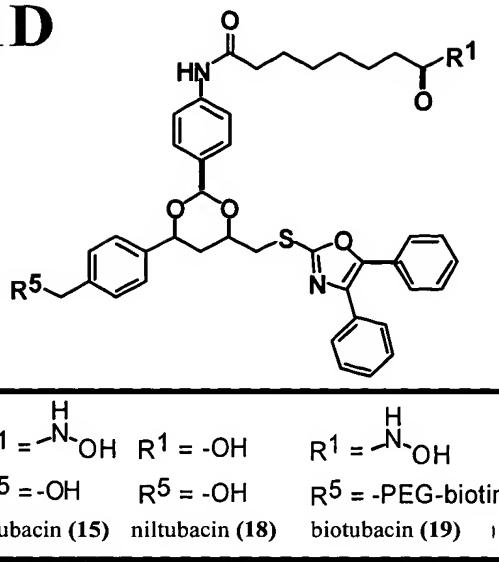
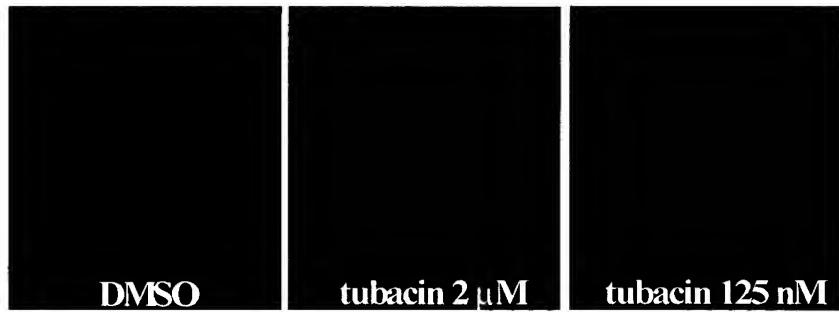
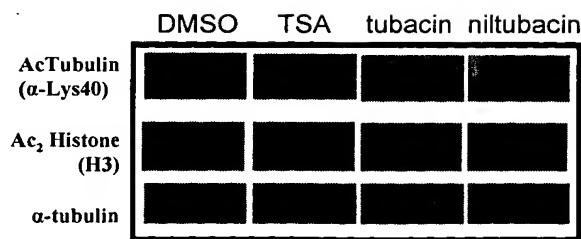
FIG. 41D**FIG. 41E****FIG. 41F**

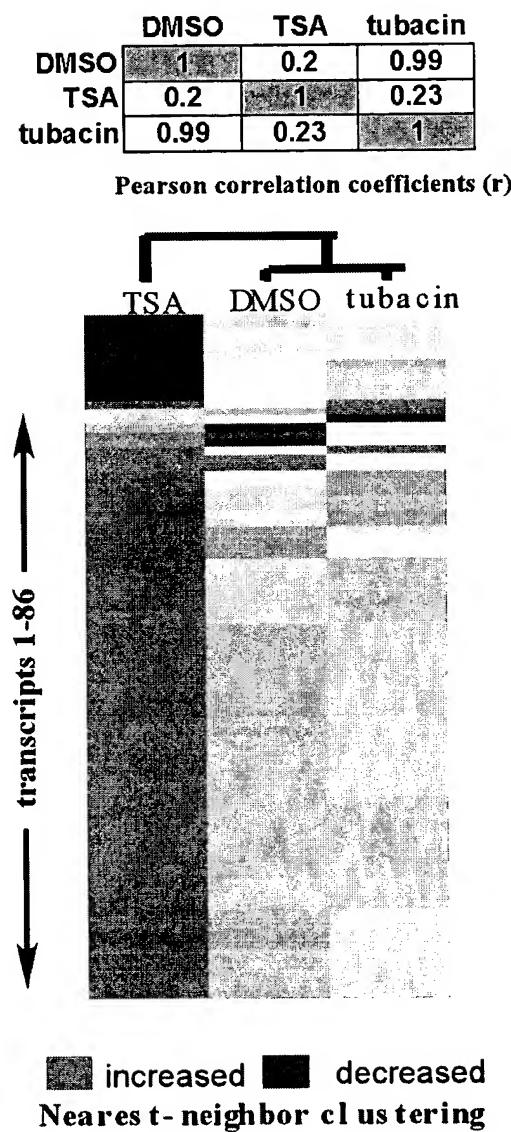
FIG. 42A

FIG. 42B

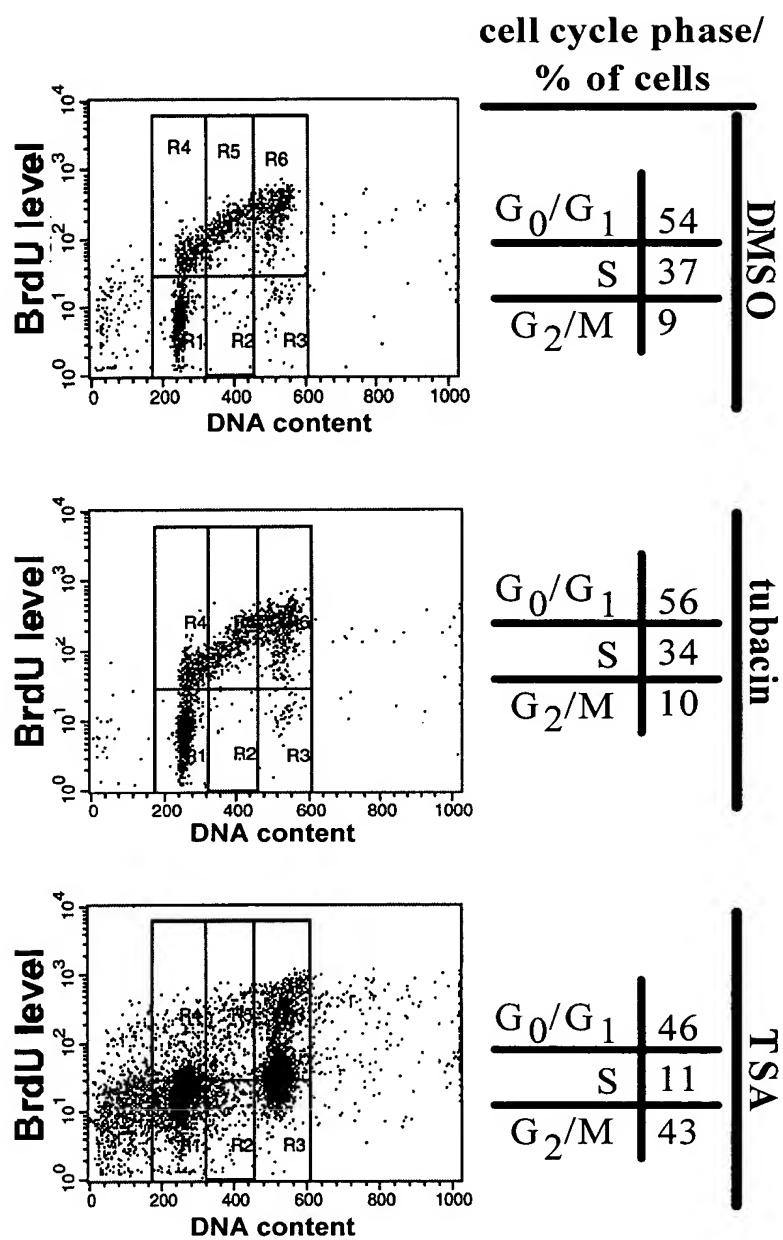


FIG. 42C

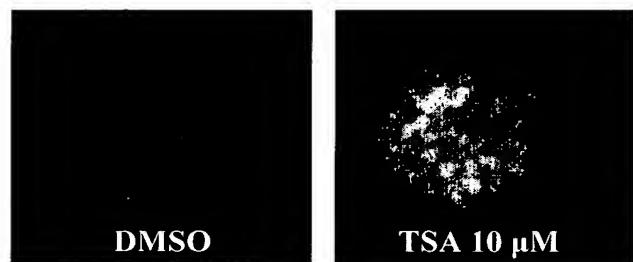


FIG. 42D

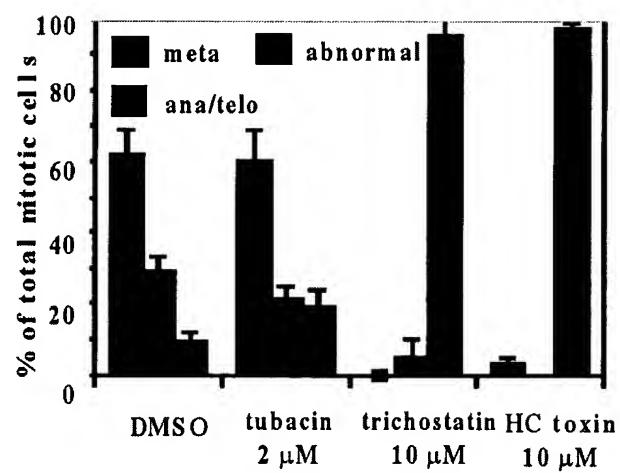


FIG. 43A

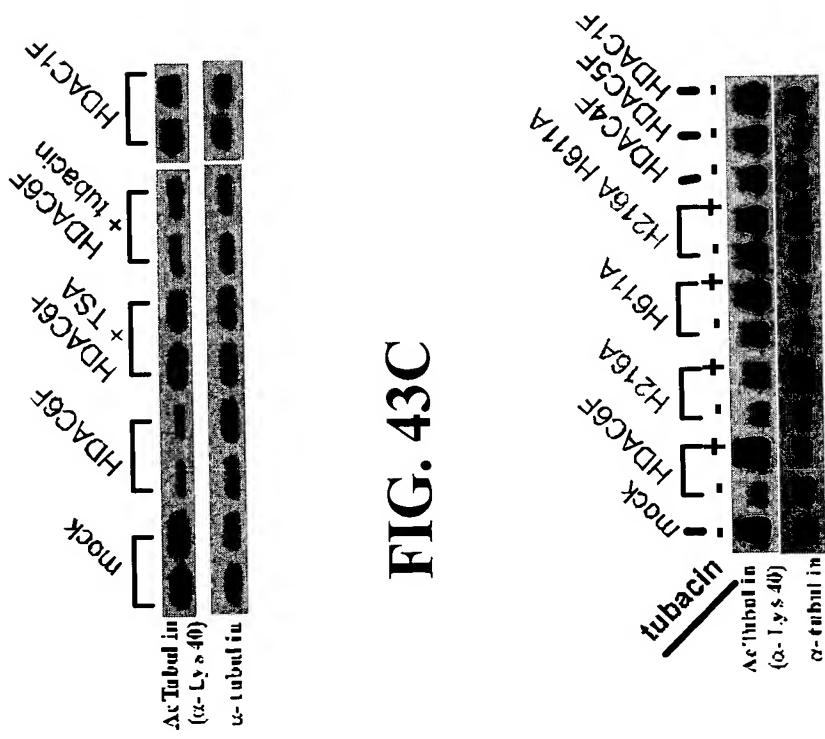


FIG. 43B

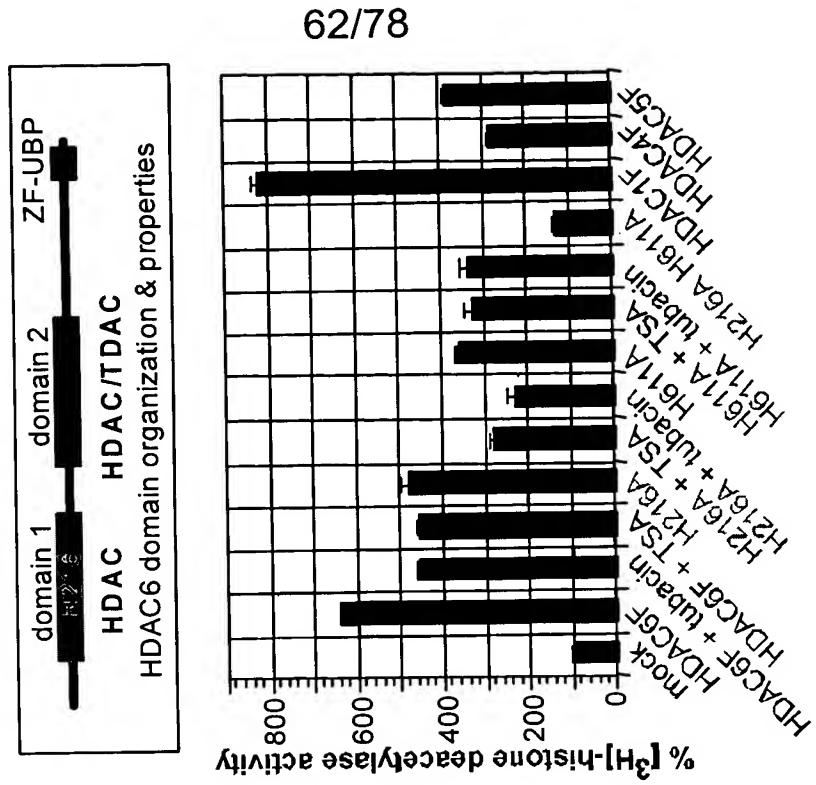


FIG. 43D

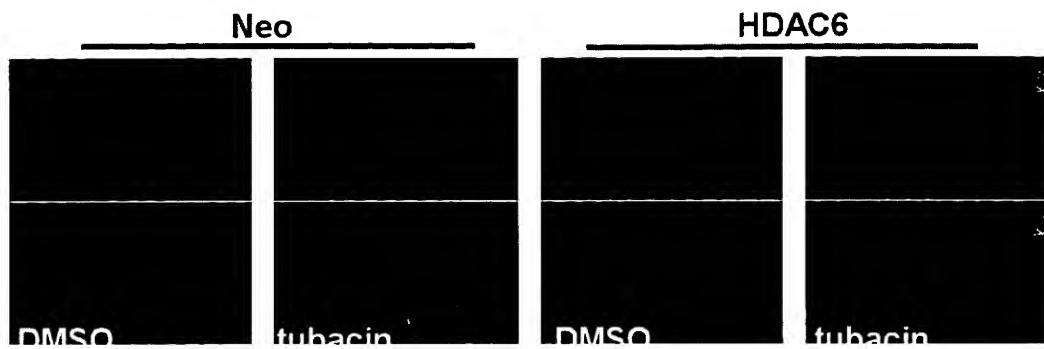


FIG. 43E



FIG. 43F

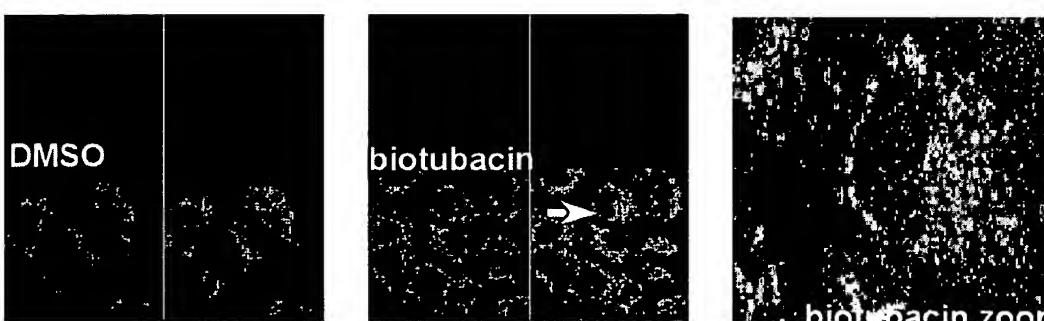


FIG. 44A

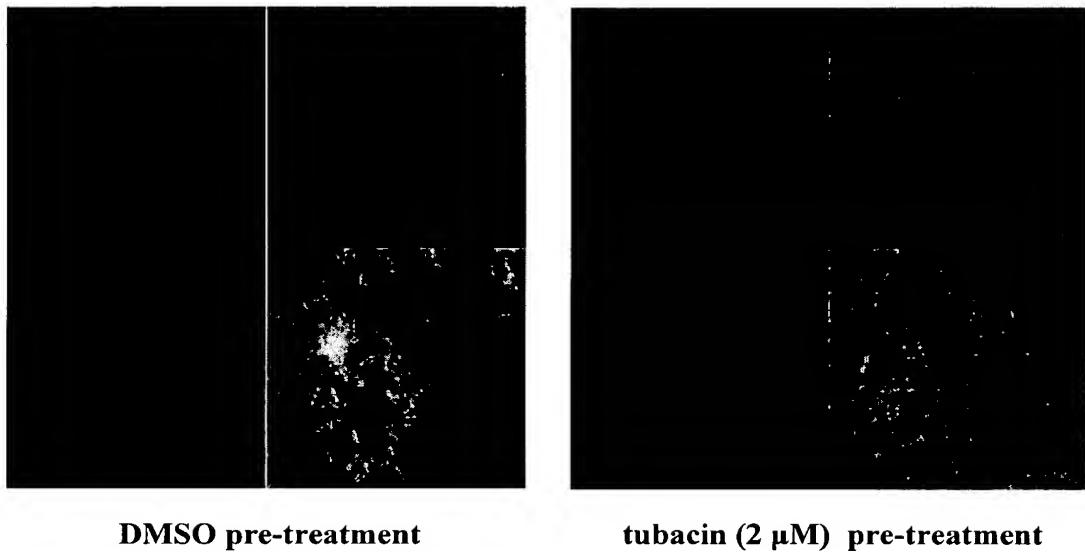


FIG. 44B

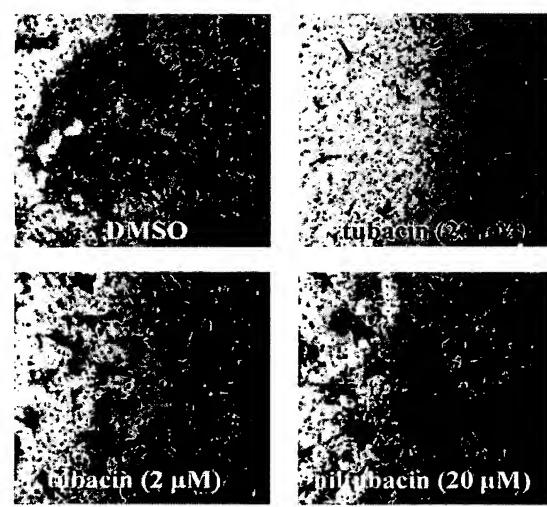


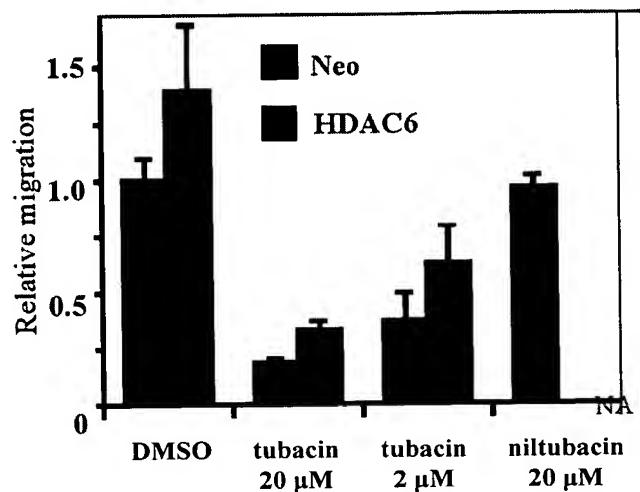
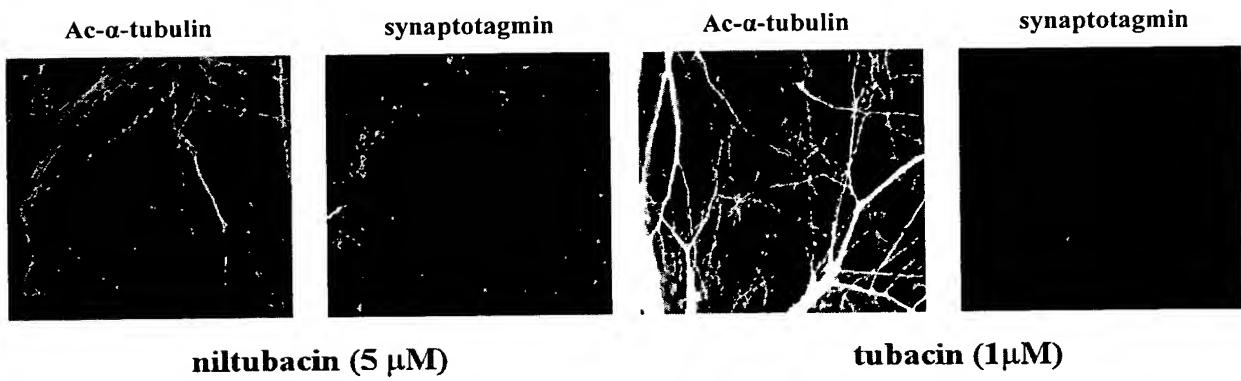
FIG. 44C**FIG. 44D**

FIG. 45A

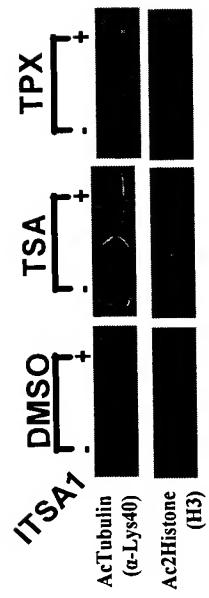
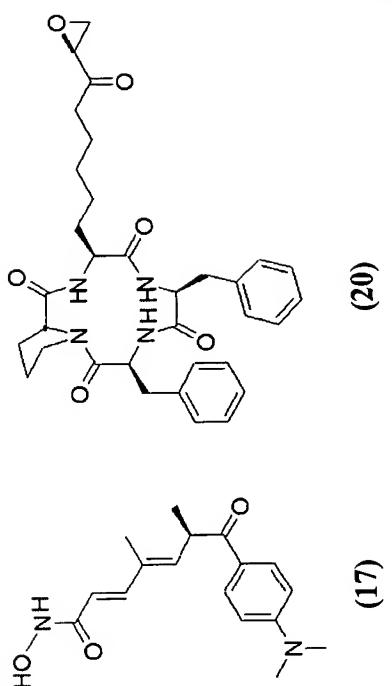


FIG. 45B



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FIG. 45C

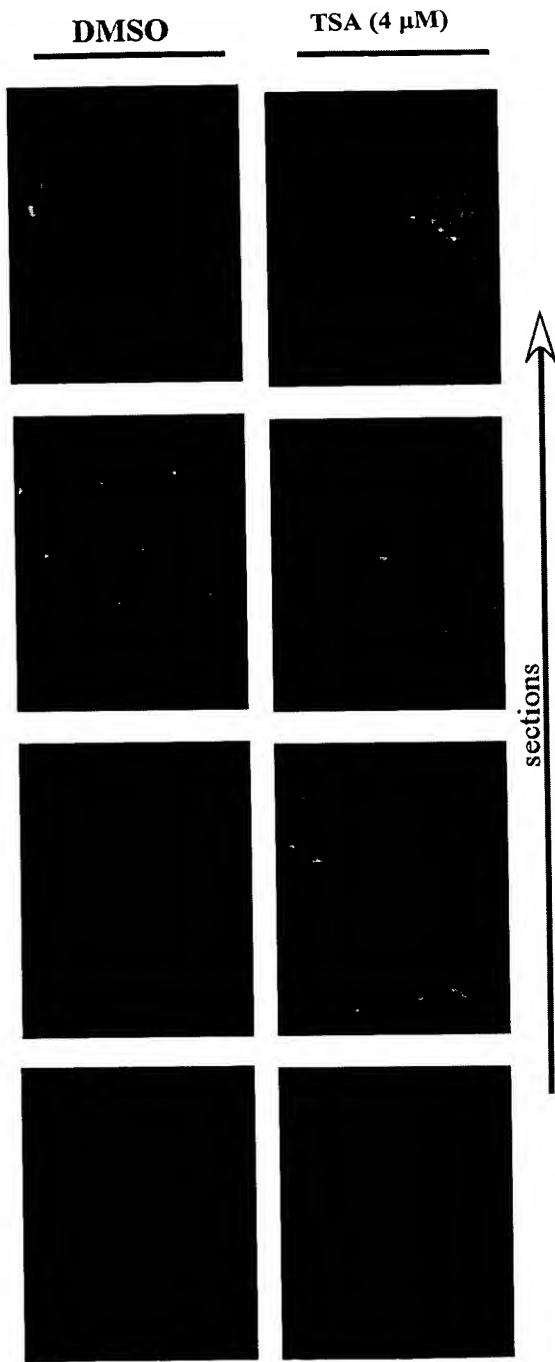
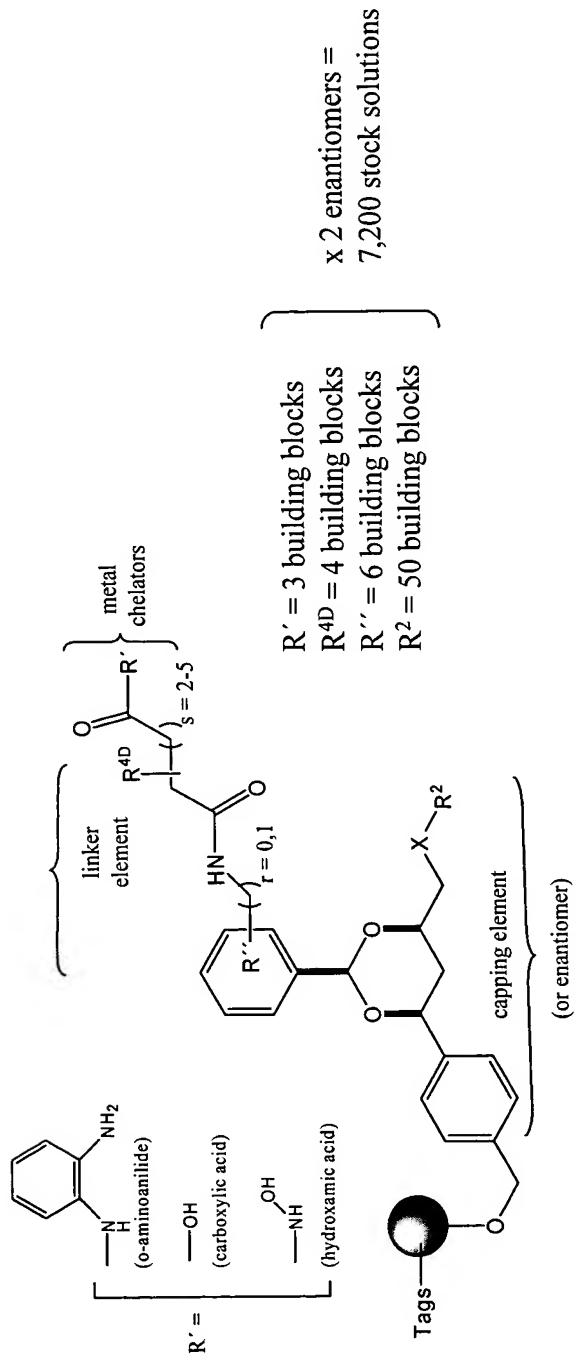


FIG. 45D



Biasing elements in diversity-oriented synthesis

FIG. 46

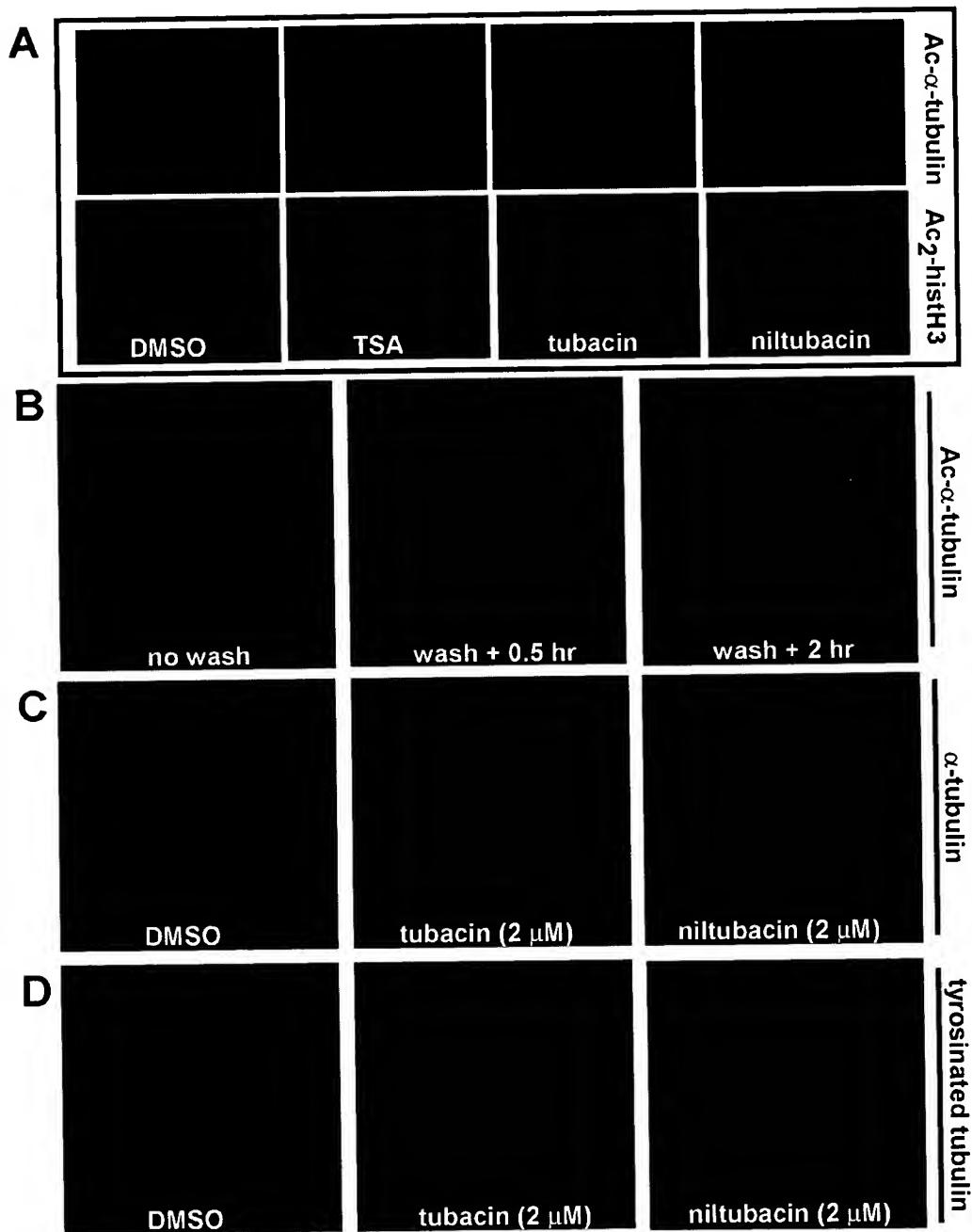


FIG. 47A

Treatment	Mean α -tubulin acetylation
DMSO	92
ITSA1	82
TSA	322
TSA + ITSA1	104
tubacin	183
tubacin + ITSA1	110

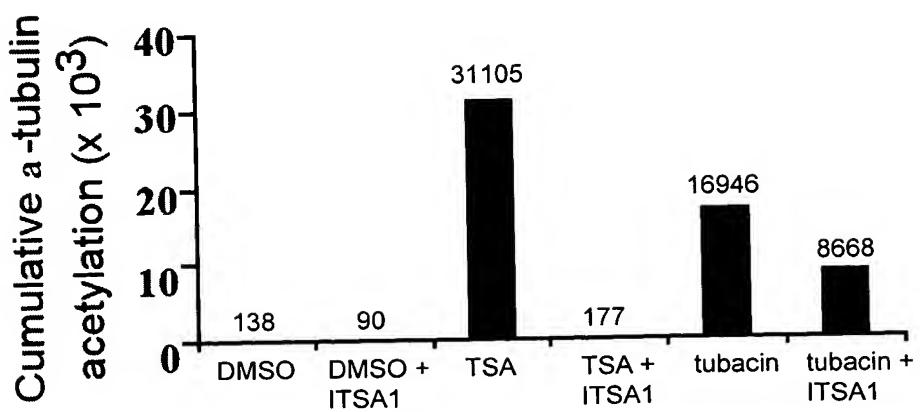
FIG. 47B

FIG. 47 C



FIG. 47 D

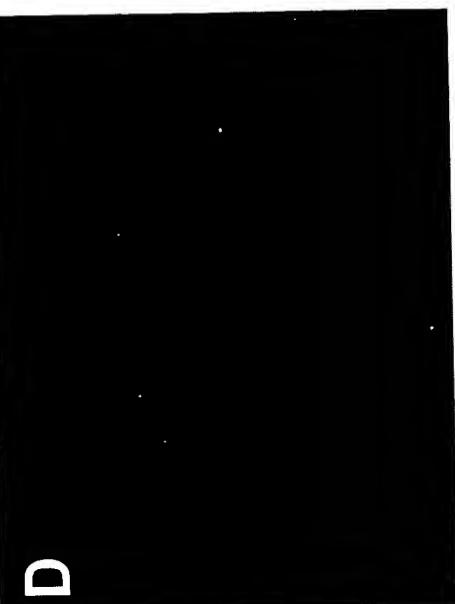


FIG. 47 E



FIG. 47 F



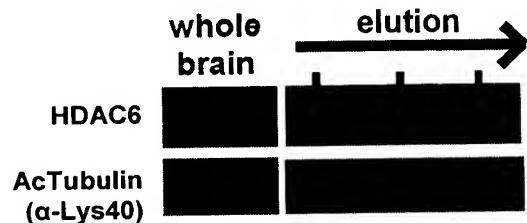
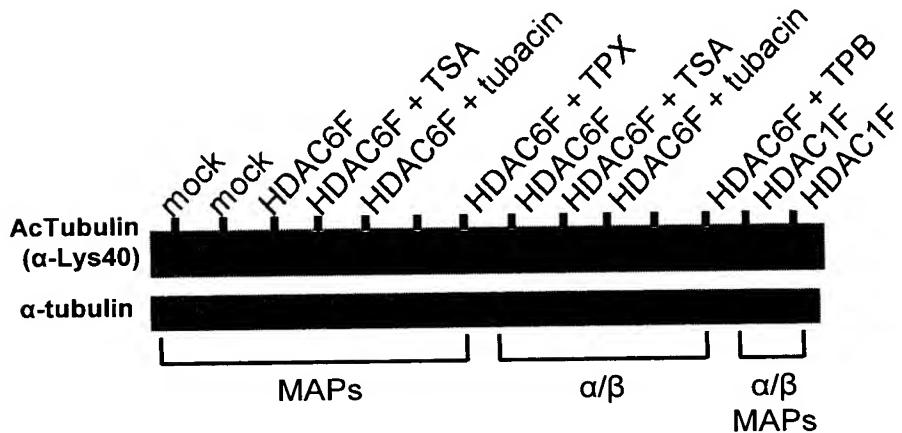
FIG. 47G**FIG. 47H**

FIG. 48A

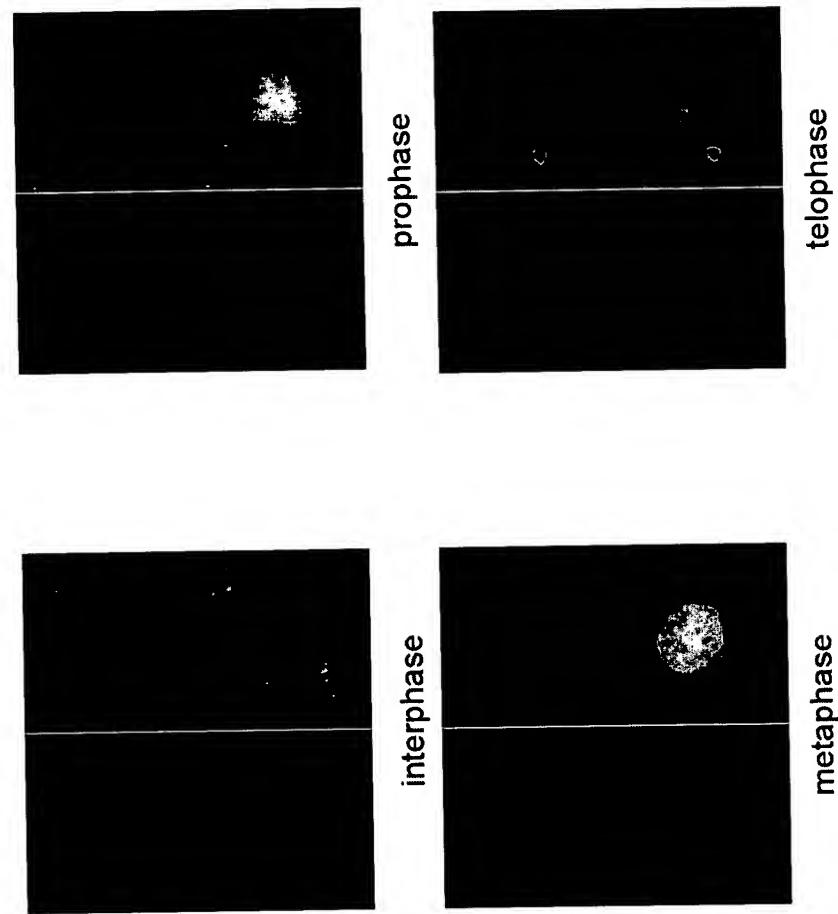


FIG. 48B

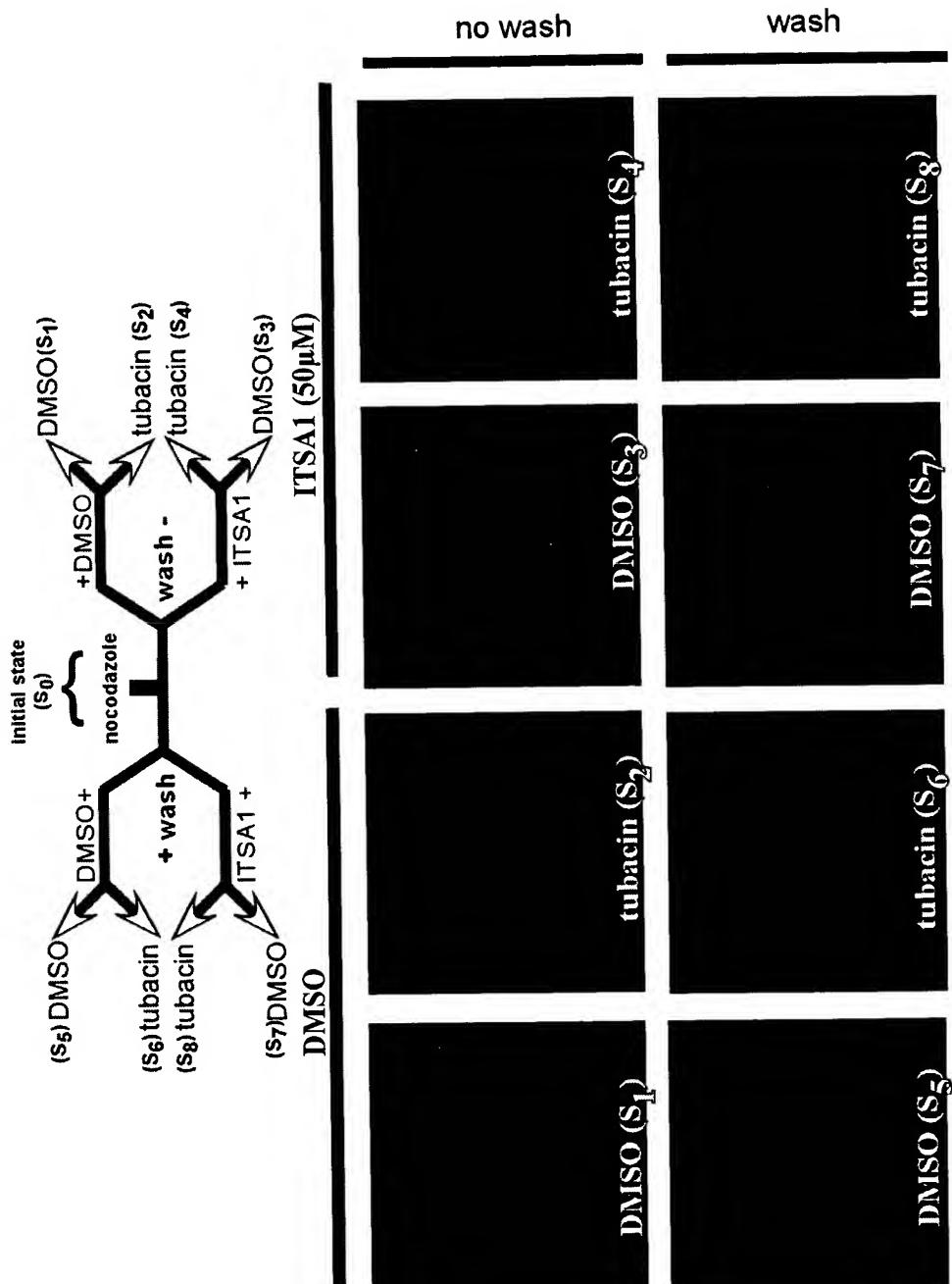


FIG. 49A

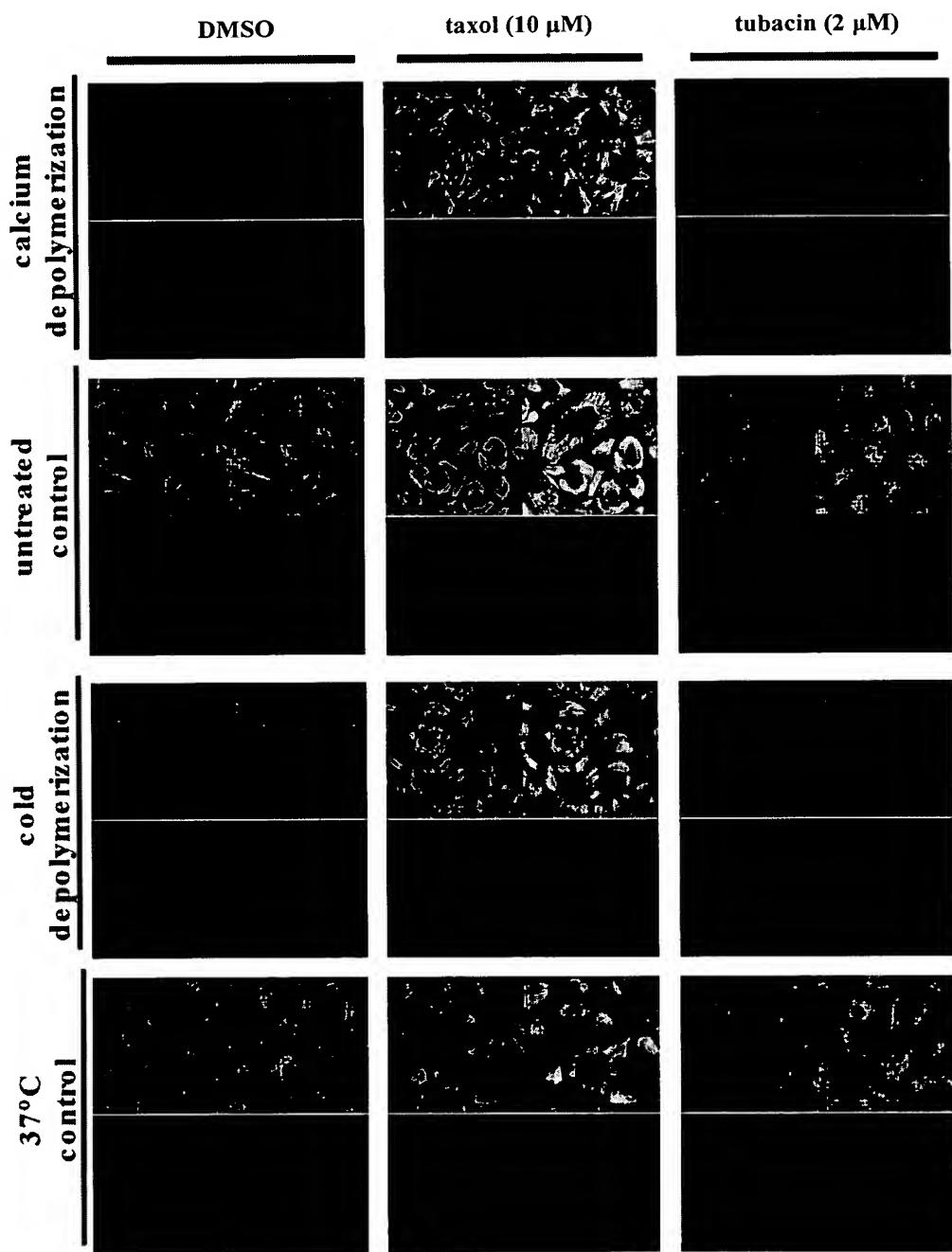


FIG. 49B

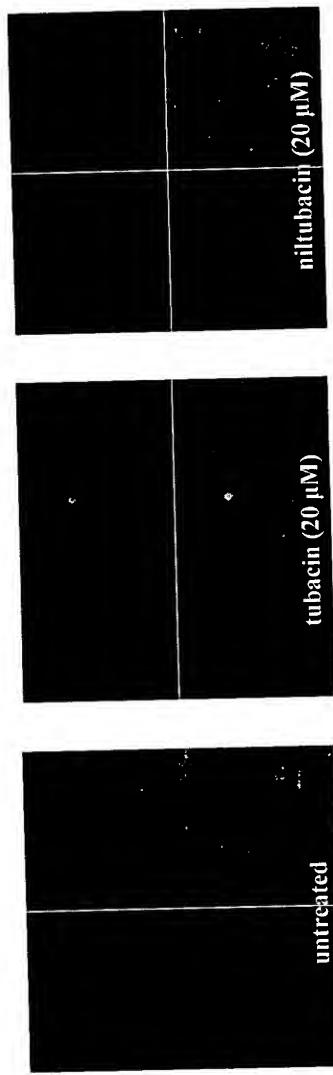


FIG. 49C

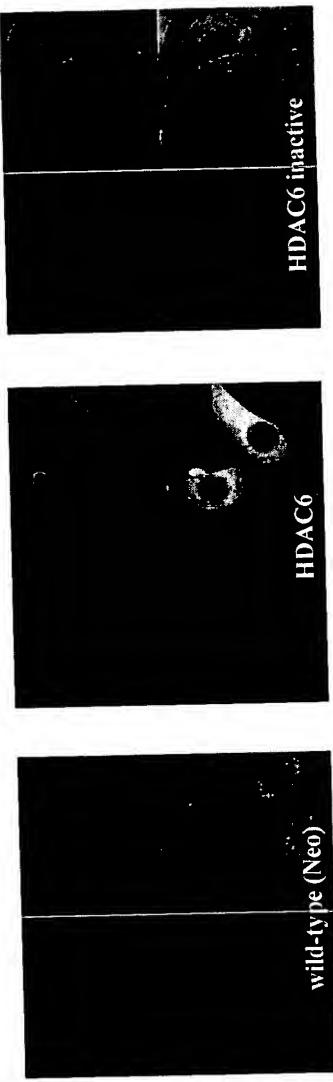


FIG. 50A

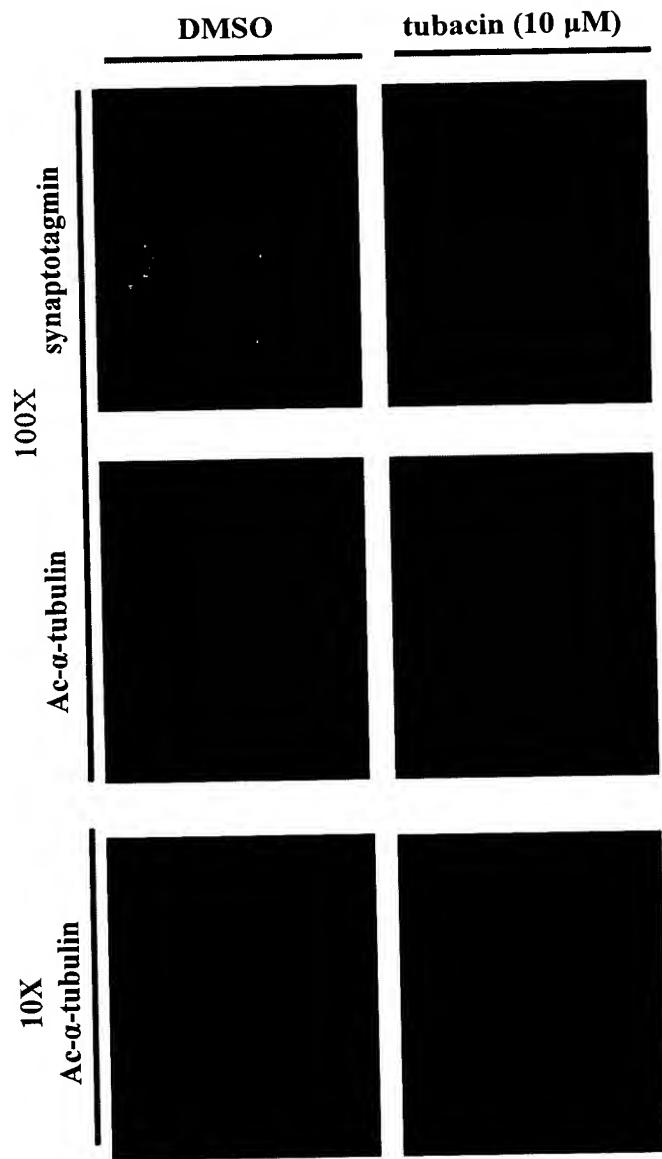


FIG. 50B

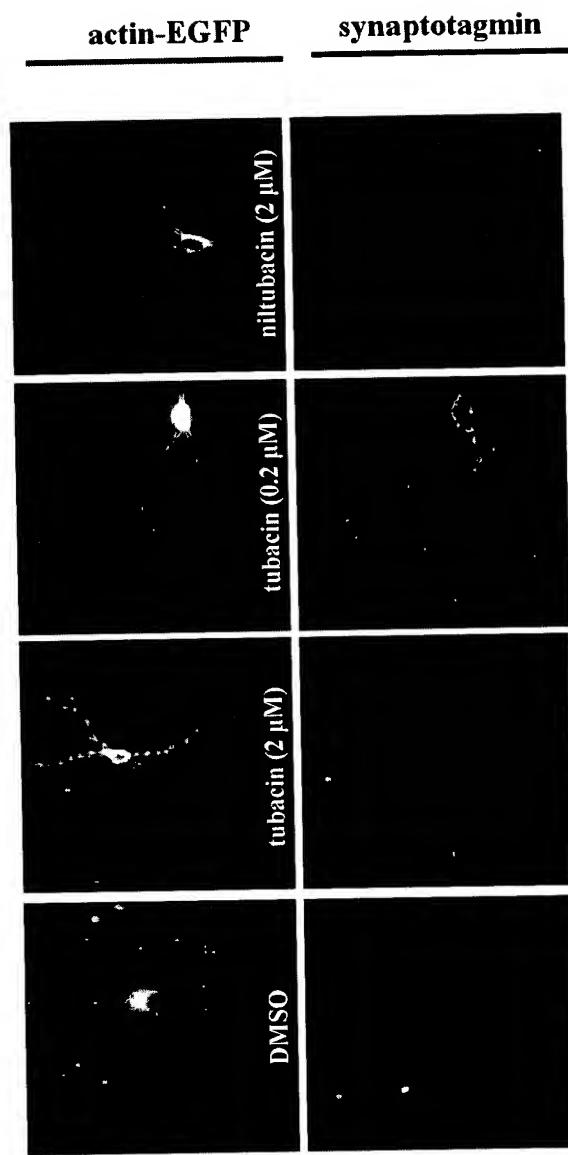
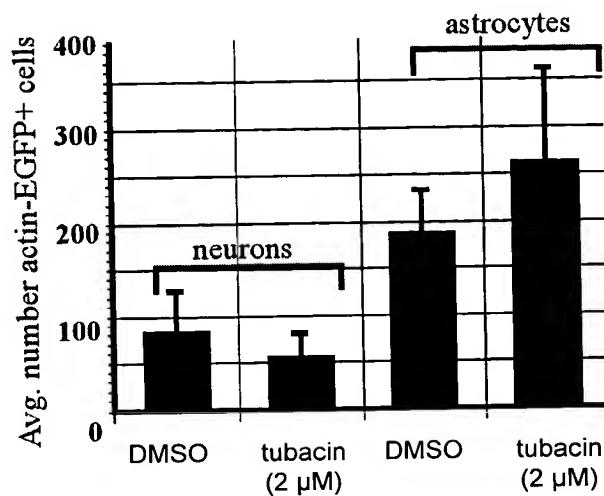


FIG. 50C**FIG. 50D**